ZUBSOLV®
(buprenorphine and naloxone) sublingual tablets
for sublingual administration
CIII
134222

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZUBSOLV® safely and effectively. See full prescribing information for ZUBSOLV.

ZUBSOLV (buprenorphine and naloxone sublingual tablets), CIII
Initial U.S. Approval: 2002

RECENT MAJOR CHANGES

Dosage and Administration (2.2)	12/2025
Dosage and Administration (2.4)	05/2025
Warnings and Precautions (5.2, 5.3)	12/2025

INDICATIONS AND USAGE

ZUBSOLV contains buprenorphine, a partial opioid agonist, and naloxone, an opioid antagonist, and is indicated for treatment of opioid dependence. (1)
ZUBSOLV should be used as part of a complete treatment plan that includes counseling and psychosocial support. (1)

DOSAGE AND ADMINISTRATION

- Following induction, ZUBSOLV is administered sublingually as a single daily dose. (2.1)
- Strongly consider recommending or prescribing an opioid overdose reversal agent (e.g., naloxone, nalmefene) at the time ZUBSOLV is initiated or renewed because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose. (2.2)
- To avoid precipitating withdrawal, induction with ZUBSOLV should be undertaken when objective and clear signs of withdrawal are evident and ZUBSOLV should be administered in divided doses when used as initial treatment. (2.3)
- For patients dependent on short-acting opioid products who are in opioid withdrawal; on Day 1, administer up to 5.7 mg/1.4 mg of ZUBSOLV (in divided doses). On Day 2, administer up to a total dose of 11.4 mg/2.9 mg of ZUBSOLV as a single dose. (2.3)
- For patients dependent on methadone or long-acting opioid products, induction onto sublingual buprenorphine monotherapy is recommended on Days 1 and 2 of treatment. (2.3)
- The maintenance dose of ZUBSOLV is generally in the range of 2.9 mg/0.71 mg to 17.2 mg/4.2 mg per day and should be based on clinical response. (2.4)
- Administer ZUBSOLV as directed in the Full Prescribing Information. (2.5)
- When discontinuing treatment, gradually taper to avoid signs and symptoms of withdrawal. (2.8)

DOSAGE FORMS AND STRENGTHS

Sublingual tablet:

- Buprenorphine 0.7 mg /naloxone 0.18 mg,
- Buprenorphine 1.4 mg /naloxone 0.36 mg,
- Buprenorphine 2.9 mg /naloxone 0.71 mg,
- Buprenorphine 5.7 mg /naloxone 1.4 mg,
- Buprenorphine 8.6 mg /naloxone 2.1 mg and
- Buprenorphine 11.4 mg /naloxone 2.9 mg. (3)

CONTRAINDICATIONS

Hypersensitivity to buprenorphine or naloxone. (4)

WARNINGS AND PRECAUTIONS

- Addiction, Abuse, and Misuse: Buprenorphine can be abused in a similar manner to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Respiratory Depression: Life-threatening respiratory depression and death have occurred in association with buprenorphine use. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with ZUBSOLV. (5.2, 5.3)
- Unintentional Pediatric Exposure: Store ZUBSOLV safely out of the sight and reach of children. Buprenorphine can cause severe and fatal respiratory depression in children. (5.4)
- Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy. (5.5)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.6)
- Risk of Opioid Withdrawal with Abrupt Discontinuation: If treatment is temporarily interrupted or discontinued, monitor patients for withdrawal and treat appropriately. (5.7)
- Risk of Hepatitis; Hepatic Events: Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.8)
- Precipitation of Opioid Withdrawal Signs and Symptoms: An opioid withdrawal syndrome is likely to occur with parenteral misuse of ZUBSOLV by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided. (5.10)
- Risk of Overdose in Opioid-Naïve Patients: ZUBSOLV is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg equivalent sublingual dose of buprenorphine. (5.11)

ADVERSE REACTIONS

Adverse events commonly observed with sublingual administration of ZUBSOLV are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Edenbridge Pharmaceuticals, LLC DBA Dexcel Pharma USA at 1-877-381-3336, or FDA at 1-800-FDA-1088, or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Benzodiazepines: Use caution in prescribing ZUBSOLV for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7)
- CYP3A4 Inhibitors and Inducers: Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7)
- Antiretrovirals: Patients who are on chronic buprenorphine treatment should have their dose monitored if NNRTIs are added to their treatment regimen. Monitor patients taking buprenorphine and atazanavir with and without ritonavir, and reduce dose of buprenorphine if warranted. (7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue ZUBSOLV if serotonin syndrome is suspected. (7)

USE IN SPECIFIC POPULATIONS

- Lactation: Buprenorphine passes into mother's milk. (8.2)
- Geriatric Patients: Monitor for sedation and Respiratory Depression. (8.5)
- Moderate and Severe Hepatic Impairment: Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZUBSOLV is indicated for treatment of opioid dependence. ZUBSOLV should be used as part of a complete treatment plan that includes counseling and psychosocial support.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

The difference in bioavailability of ZUBSOLV compared to Suboxone® sublingual tablet requires a different tablet strength to be given to the patient. One ZUBSOLV 5.7 mg/1.4 mg sublingual tablet provides equivalent buprenorphine exposure to one Suboxone 8 mg/2 mg sublingual tablet.
Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits.

2.2 Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene) and discuss the importance of having access to an opioid overdose reversal agent. Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider recommending or prescribing an overdose reversal agent for the emergency treatment of opioid overdose, both when initiating and renewing treatment with ZUBSOLV. Also consider recommending or prescribing such an agent if the patient has household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose *[see Warnings and Precautions (5.2)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Warnings and Precautions (5.2)]*.
There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Advise patients and caregivers that opioid overdose reversal agents, such as naloxone or nalmefene, may also be administered for a known or suspected overdose with ZUBSOLV itself. Higher than normal doses and repeated administration of an opioid overdose reversal agent may be necessary due to the long duration of action of ZUBSOLV and its affinity for the mu receptor *[see Overdosage (10)]*.

2.3 Induction

Prior to induction, consideration should be given to the type of opioid dependence i.e., long- or short-acting opioid products, the time since last opioid use, and the degree or level of opioid dependence.

Patients dependent on heroin or other short-acting opioid products
Patients dependent on heroin or other short-acting opioid products may be induced with either ZUBSOLV or with sublingual buprenorphine monotherapy. At treatment initiation, the first dose of ZUBSOLV should be administered when objective signs of moderate opioid withdrawal appear, not less than six hours after the patient last used opioids, to avoid precipitating an opioid withdrawal syndrome.

It is recommended that an adequate treatment dose, titrated to clinical effectiveness, be achieved as rapidly as possible. In some studies, a too-gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period.

On Day 1, an induction dosage of up to 5.7 mg/1.4 mg ZUBSOLV is recommended. Clinicians should start with an initial dose of 1.4 mg/0.36 mg ZUBSOLV. The remainder of the Day 1 dose of up to 4.2 mg/1.08 mg should be divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2 hour intervals. Some patients (e.g., those with recent exposure to buprenorphine) may tolerate up to 3 x 1.4 mg/0.36 mg ZUBSOLV as a single, second dose.

On Day 2, a single daily dose of up to 11.4 mg/2.9 mg ZUBSOLV is recommended.

Patients dependent on methadone or long-acting opioid products
Patients dependent on methadone or long-acting opioid products may be more susceptible to precipitated and prolonged withdrawal during induction than those on short-acting opioid products.
Buprenorphine/naloxone combination products have not been evaluated in adequate and well-controlled studies for induction in patients who are physically dependent on long-acting opioid products, and the naloxone in these combination products is absorbed in small amounts by the sublingual route and could cause worse precipitated and prolonged withdrawal. For this reason, buprenorphine monotherapy is recommended in patients taking long-acting opioids when used according to approved administration instructions. Following induction, the patient may then be transitioned to once-daily ZUBSOLV.

2.4 Maintenance

- The dosage of ZUBSOLV from Day 3 onwards should be progressively adjusted in increments/decrements of 2.9 mg/0.71 mg or lower of buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- After treatment induction to the recommended dose of 11.4 mg/2.9 mg buprenorphine/naloxone per day, dosing should be further adjusted based on the individual patient and clinical response. The maintenance dose of ZUBSOLV is generally in the range of 2.9 mg/0.71 mg buprenorphine/naloxone to 17.2 mg/4.2 mg buprenorphine/naloxone per day. Dosages higher than 17.2 mg/4.2 mg buprenorphine/naloxone daily have not been investigated in randomized clinical trials but may be appropriate for some patients.
- When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.
- There is no maximum recommended duration of maintenance treatment. Patients may require treatment indefinitely and should continue for as long as patients are benefiting and the use of ZUBSOLV contributes to the intended treatment goals.

2.5 Method of Administration

ZUBSOLV must be administered whole. Do not cut, chew, or swallow ZUBSOLV. Advise patients not to eat or drink anything until the tablet is completely dissolved. ZUBSOLV should be placed under the tongue until dissolved. The dissolve time for ZUBSOLV varies between individuals, and the median dissolve time observed was 5 minutes. For dosages requiring more than one sublingual tablet, place all tablets in different places under the tongue at the same time. Patients should keep the tablets under the tongue until dissolved; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.
If a sequential mode of administration is preferred, patients should follow the same manner of dosing to ensure consistency in bioavailability.

Proper administration technique should be demonstrated to the patient.

Advise patients to do the following after the product has completely dissolved in the oral mucosa: take a sip of water, swish gently around the teeth and gums, and swallow. Advise patients to wait for at least one hour after taking ZUBSOLV before brushing teeth *[see Warnings and Precautions (5.13), Postmarketing Experience (6.2), Information for Patients (17), and the Medication Guide]*.

2.6 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. ZUBSOLV is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.
Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.
Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the healthcare provider's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity
2. Absence of medical or behavioral adverse effects
3. Responsible handling of medications by the patient
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use)

If treatment goals are not being achieved, the healthcare provider should re-evaluate the appropriateness of continuing the current treatment.

2.7 Unstable Patients

Healthcare providers will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the healthcare provider does not feel that he/she has the expertise to manage the patient. In such cases, the healthcare provider may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

2.8 Discontinuing Treatment

The decision to discontinue therapy with ZUBSOLV after a period of maintenance should be made as part of a comprehensive treatment plan. Advise patients of the potential to relapse to illicit drug use following discontinuation of opioid agonist/partial agonist medication-assisted treatment. Taper patients to avoid the occurrence of withdrawal signs and symptoms *[see Warnings and Precautions (5.7)]*.

2.9 Switching between ZUBSOLV Sublingual Tablets and Other Buprenorphine/Naloxone Combination Products

For patients being switched between ZUBSOLV and other buprenorphine/naloxone products dosage adjustments may be necessary. Patients should be monitored for over-medication as well as withdrawal or other signs of under-dosing.

The differences in bioavailability of ZUBSOLV compared to Suboxone tablet require that different tablet strengths be given to the patient. One ZUBSOLV 5.7 mg/1.4 mg sublingual tablet provides equivalent buprenorphine exposure to one Suboxone 8 mg/2 mg sublingual tablet.

When switching between Suboxone dosage strengths and ZUBSOLV dosage strengths the corresponding dosage strengths are:

Suboxone sublingual tablets, including generic equivalents	Corresponding dosage strength of ZUBSOLV sublingual tablets
One 2 mg/0.5 mg sublingual buprenorphine/naloxone tablet	One 1.4 mg/0.36 mg ZUBSOLV sublingual tablet
4 mg/1 mg buprenorphine/naloxone taken as: • Two 2 mg/0.5 mg sublingual buprenorphine/naloxone tablets	One 2.9 mg/0.71 mg ZUBSOLV sublingual tablet
One 8 mg/2 mg sublingual buprenorphine/naloxone tablet	One 5.7 mg/1.4 mg ZUBSOLV sublingual tablet
12 mg/3 mg buprenorphine/naloxone, taken as: • One 8 mg/2 mg sublingual buprenorphine/naloxone tablet AND • Two 2 mg/0.5 mg sublingual buprenorphine/naloxone tablets	One 8.6 mg/2.1 mg ZUBSOLV sublingual tablet
16 mg/4 mg buprenorphine/naloxone, taken as: • Two 8 mg/2 mg sublingual buprenorphine/naloxone tablets	One 11.4 mg/2.9 mg ZUBSOLV sublingual tablet

3 DOSAGE FORMS AND STRENGTHS

ZUBSOLV sublingual tablet is supplied in six dosage strengths:

- Buprenorphine 0.7 mg /naloxone 0.18 mg, white, oval shape tablets imprinted with ".7"
- Buprenorphine 1.4 mg /naloxone 0.36 mg, white, triangular shape tablets imprinted with "1.4"
- Buprenorphine 2.9 mg /naloxone 0.71 mg, white, D shape tablets imprinted with "2.9"
- Buprenorphine 5.7 mg /naloxone 1.4 mg, white, round shape tablets imprinted with "5.7"
- Buprenorphine 8.6 mg /naloxone 2.1 mg, white, diamond shape tablets imprinted with "8.6"
- Buprenorphine 11.4 mg /naloxone 2.9 mg, white, capsule shape tablets imprinted with "11.4"

4 CONTRAINDICATIONS

ZUBSOLV is contraindicated in patients with a history of hypersensitivity to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported *[see Warnings and Precautions (5.9)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse and Misuse

ZUBSOLV contains buprenorphine, a schedule III controlled substance that can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. 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 *[see Drug Abuse and Dependence (9.2)]*.

5.2 Risk of Life-Threatening Respiratory and Central Nervous System (CNS) Depression

Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with ZUBSOLV *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.
Use ZUBSOLV with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).
Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)]*.
Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.8)]*.
Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose
Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene) and discuss the importance of having access to an opioid overdose reversal agent. Because patients being treated for opioid use disorder have the potential for relapse, putting them at risk for opioid overdose, strongly consider recommending or prescribing an opioid overdose reversal agent for the emergency treatment of an opioid overdose, both when initiating and renewing treatment with ZUBSOLV. Also consider recommending or prescribing such an agent if the patient has household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose *[see Dosage and Administration (2.2)]*.
Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).
There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.
Advise patients and caregivers that an opioid overdose reversal agent, such as naloxone or nalmefene may also be administered for a known or suspected overdose with ZUBSOLV itself. Higher than normal doses and repeated administration of an opioid reversal agent may be necessary due to the long duration of action of ZUBSOLV and its affinity for the mu receptor *[see Overdosage (10)]*.
Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered.

5.3 Managing Risks from Concomitant Use of Benzodiazepines or Other CNS Depressants

Concomitant use of buprenorphine and benzodiazepines and/or other CNS depressants (e.g., alcohol, non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids) increases the risk of adverse reactions including overdose, respiratory depression, and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.
As a routine part of orientation to buprenorphine treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, and alcohol.
Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of buprenorphine treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of buprenorphine as a strategy to address benzodiazepine use in buprenorphine-treated patients. However, if a patient is sedated at the time of buprenorphine dosing, delay or omit the buprenorphine dose if appropriate.
Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.
For patients on buprenorphine treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use.
If concomitant use is warranted, strongly consider recommending or prescribing an opioid overdose reversal agent, as is recommended for all patients on buprenorphine treatment for opioid use disorder *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.
In addition, take measures to confirm that patients are taking their medications as prescribed and are not diverting or supplementing with illicit drugs. Toxicology screening should test for prescribed and illicit benzodiazepines *[see Drug Interactions (7)]*.

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause fatal respiratory depression in children who are accidentally exposed to it. Store buprenorphine containing medications safely out of the sight and reach of children and destroy any unused medication appropriately *[see Patient Counseling Information (17)]*.

5.5 Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly *[see Use in Specific Populations 8.1)]*.
Advise pregnant women receiving opioid addiction treatment with ZUBSOLV of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*. This risk must be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance and benefits of management of opioid addiction throughout pregnancy.

5.6 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.7 Risk of Opioid Withdrawal with Abrupt Discontinuation

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. When discontinuing ZUBSOLV, gradually taper the dosage *[see Dosage and Administration 2.8)]*.

5.8 Risk of Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, ZUBSOLV may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.9 Hypersensitivity Reactions

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of ZUBSOLV.

5.10 Precipitation of Opioid Withdrawal Signs and Symptoms

Because it contains naloxone, ZUBSOLV is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Because of the partial agonist properties of buprenorphine, ZUBSOLV may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

5.11 Risk of Overdose in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. ZUBSOLV is not appropriate as an analgesic.

5.12 Use in Patients with Impaired Hepatic Function

Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. The doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated, and hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine's efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in subjects with severe hepatic impairment. However, buprenorphine/naloxone products are not recommended for initiation of treatment (induction) in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. Buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. Patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy *[see Use in Specific Populations (8.6)]*.

5.13 Dental Adverse Events

Cases of dental caries, some severe (i.e., tooth fracture, tooth loss), have been reported following the use of transmucosal buprenorphine-containing products. Reported events include cavities, tooth decay, dental abscesses/infection, rampant caries, tooth erosion, fillings falling out, and, in some cases, total tooth loss. Treatment for these events included tooth extraction, root canal, dental surgery, as well as other restorative procedures (i.e., fillings, crowns, implants, dentures). Multiple cases were reported in individuals without any prior history of dental problems.
Refer patients to dental care services and encourage them to have regular dental checkups while taking ZUBSOLV. Educate patients to seek dental care and strategies to maintain or improve oral health while being treated with transmucosal buprenorphine-containing products. Strategies include, but are not limited to, gently rinsing the teeth and gums with water and then swallowing after ZUBSOLV has been completely dissolved in the oral mucosa. Advise patients to wait for at least one hour after taking ZUBSOLV before brushing teeth *[see Dosing and Administration (2.5), Information for Patients (17), Medication Guide]*.

5.14 QTc Prolongation

Thorough QT studies with buprenorphine products have demonstrated QT prolongation ≤15 msec. This QTc prolongation effect does not appear to be mediated by hERG channels. Based on these two findings, buprenorphine is unlikely to be pro-arrhythmic when used alone in patients without risk factors. The risk of combining buprenorphine with other QT prolonging agents is not known.
Consider these observations in clinical decisions when prescribing ZUBSOLV to patients with risk factors such as hypokalemia, bradycardia, recent conversion from atrial fibrillation, congestive heart failure, digitalis therapy, baseline QT prolongation, subclinical long-QT syndrome, or severe hypomagnesemia.

5.15 Impairment of Ability to Drive or Operate Machinery

ZUBSOLV may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Caution patients about driving or operating hazardous machinery until they are reasonably certain that ZUBSOLV therapy does not adversely affect his or her ability to engage in such activities.

5.16 Orthostatic Hypotension

Like other opioids, ZUBSOLV may produce orthostatic hypotension in ambulatory patients.

5.17 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.18 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.19 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Respiratory and CNS Depression *[see Warnings and Precautions (5.2, 5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.6)]*
- Opioid Withdrawal *[see Warnings and Precautions (5.7, 5.10)]*
- Hepatitis, Hepatic Events *[see Warnings and Precautions (5.8)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.9)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.16)]*
- Elevation of Cerebrospinal Fluid Pressure *[see Warnings and Precautions (5.17)]*
- Elevation of Intracholedochal Pressure *[see Warnings and Precautions (5.18)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ZUBSOLV for use as initial treatment was evaluated in two clinical trials that had identical, blinded, two-day induction phases, comparing ZUBSOLV to generic buprenorphine. On the first day, subjects received an initial dose of ZUBSOLV 1.4 mg/0.36 mg or generic buprenorphine 2 mg, followed by ZUBSOLV 4.2 mg/1.08 mg or generic buprenorphine 6 mg 1.5 hours later. In total, safety data were available for 538 opioid-dependent subjects exposed to ZUBSOLV (buprenorphine/naloxone) sublingual tablets when used for initial treatment.

Table 1. Adverse Reactions in ≥ 5% of Patients During the Induction Phase by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	**ZUBSOLV (N=538)**	**Generic BUP (N=530)**	**Overall (N=1068)**
	N (%)		
Patients with any Adverse Reactions	139 (26%)	136 (26%)	275 (26%)
Gastrointestinal Disorders	64 (12%)	60 (11%)	124 (12%)
Nausea	29 (5%)	36 (7%)	65 (6%)
Vomiting	25 (5%)	26 (5%)	51 (5%)
Nervous System Disorders	48 (9%)	44 (8%)	92 (9%)
Headache	36 (7%)	35 (7%)	71 (7%)

BUP = buprenorphine
ZUBSOLV = buprenorphine/naloxone

The safety of buprenorphine/naloxone for longer-term use (up to 16 weeks of treatment) was evaluated in previous studies in 497 opioid-dependent subjects. The prospective evaluation of buprenorphine/naloxone was supported by clinical trials using buprenorphine tablets without naloxone and other trials using buprenorphine sublingual solutions. In total, safety data were available from 3214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction. See Table 2.

Table 2. Adverse Events > 5% by Body System and Treatment Group in a 4-week Study

	N (%)	**N (%)**
Body System / Adverse Event (COSTART Terminology)	**Buprenorphine/naloxone 16/4 mg/day N=107**	**Placebo N=107**
Body as a Whole		
Asthenia	7 (7%)	7 (7%)
Chills	8 (8%)	8 (8%)
Headache	39 (37%)	24 (22%)
Infection	6 (6%)	7 (7%)
Pain	24 (22%)	20 (19%)
Pain Abdomen	12 (11%)	7 (7%)
Pain Back	4 (4%)	12 (11%)
Withdrawal Syndrome	27 (25%)	40 (37%)
Cardiovascular System		
Vasodilation	10 (9%)	7 (7%)
Digestive System		
Constipation	13 (12%)	3 (3%)
Diarrhea	4 (4%)	16 (15%)
Nausea	16 (15%)	12 (11%)
Vomiting	8 (8%)	5 (5%)
Nervous System		
Insomnia	15 (14%)	17 (16%)
Respiratory System		
Rhinitis	5 (5%)	14 (13%)
Skin and Appendages		
Sweating	15 (14%)	11 (10%)

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in four months of treatment. Table 3 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled study.

Table 3. Adverse Events (≥ 5%) by Body System and Treatment Group in a 16-week Study

Body System / Adverse Event (COSTART Terminology)	**Buprenorphine dose***				
	Very Low* (N=184)	**Low* (N=180)**	**Moderate* (N=186)**	**High* (N=181)**	**Total* (N=731)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome.	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
"Very low" dose (1 mg solution) would be less than a tablet dose of 2 mg
"Low" dose (4 mg solution) approximates a 6 mg tablet dose
"Moderate" dose (8 mg solution) approximates a 12 mg tablet dose
"High" dose (16 mg solution) approximates a 24 mg tablet dose

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of buprenorphine and naloxone sublingual tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate a causal relationship to drug exposure.

The most frequently reported post-marketing adverse event not observed in clinical trials was peripheral edema.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in ZUBSOLV.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

Local reactions: Dental decay (including caries, tooth fracture, and tooth loss), glossodynia, glossitis, oral mucosal erythema, oral hypoesthesia, and stomatitis.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).
Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term.

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with ZUBSOLV.

Table 4. Clinically Significant Drug Interactions with ZUBSOLV

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of benzodiazepines and other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments *[see Warnings and Precautions (5.2, 5.3)]*. If concomitant use is warranted, strongly consider recommending or prescribing an opioid overdose reversal agent, as is recommended for all patients on buprenorphine treatment for opioid use disorder *[see Warnings and Precautions (5.2)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol.
Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of ZUBSOLV is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.
Intervention:	If concomitant use is necessary, consider dosage reduction of ZUBSOLV until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the ZUBSOLV dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir).
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine *[see Clinical Pharmacology (12.3)]*, potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the ZUBSOLV dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider ZUBSOLV dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin.
Antiretrovirals: Non-Nucleoside Reverse Transcriptase inhibitors (NNRTIs)	
Clinical Impact:	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.
Intervention:	Patients who are on chronic ZUBSOLV treatment should have their dose monitored if NNRTIs are added to their treatment regimen.
Examples:	Efavirenz, nevirapine, etravirine, delavirdine.
Antiretrovirals: Protease Inhibitors (PIs)	
Clinical Impact:	Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly.
Intervention:	Monitor patients taking ZUBSOLV and atazanavir with and without ritonavir, and reduce dose of ZUBSOLV if warranted.
Examples:	Atazanavir, ritonavir.
Antiretrovirals: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
Clinical Impact:	Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.
Intervention:	None.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ZUBSOLV if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*
Intervention:	The use of ZUBSOLV is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	Phenelzine, tranylcypromine, linezolid.
Muscle Relaxants	
Clinical Impact:	Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients receiving muscle relaxants and ZUBSOLV for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of ZUBSOLV and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, strongly consider recommending or prescribing an opioid overdose reversal agent, as is recommended for all patients on buprenorphine treatment for opioid use disorder. *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*.
Examples:	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when ZUBSOLV is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data on use of buprenorphine, one of the active ingredients in ZUBSOLV, in pregnancy, are limited; however, these data do not indicate an increased risk of major malformations specifically due to buprenorphine exposure. There are limited data from randomized clinical trials in women maintained on buprenorphine that were not designed appropriately to assess the risk of major malformations *[see Data]*. Observational studies have reported on congenital malformations among buprenorphine-exposed pregnancies, but were also not designed appropriately to assess the risk of congenital malformations specifically due to buprenorphine exposure *[see Data]*. The extremely limited data on sublingual naloxone exposure in pregnancy are not sufficient to evaluate a drug-associated risk.

Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant and higher doses. Embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 6 and 0.3 times, respectively, the human sublingual dose of 16 mg/day of buprenorphine. Pre- and post-natal development studies in rats demonstrated increased neonatal deaths at 0.3 times and above and dystocia at approximately 3 times the human sublingual dose of 16 mg/day of buprenorphine. No clear teratogenic effects were seen when buprenorphine was administered during organogenesis with a range of doses equivalent to or greater than the human sublingual dose of 16 mg/day of buprenorphine. However, increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 0.6 and approximately equal to the human sublingual dose of 16 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalus and omphalocele were also observed but these findings were not clearly treatment-related *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and Embryo-fetal Risk

Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

Dose Adjustment during Pregnancy and the Postpartum Period

Dosage adjustments of buprenorphine, such as using higher doses, may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Dosing should be based on individual response, and withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary.

Fetal/neonatal Adverse Reactions

Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with ZUBSOLV.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.5)]*.

Labor or Delivery

Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

Data

Human Data

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited data from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy do not indicate an increased risk of major malformations specifically due to buprenorphine. Several factors may complicate the interpretation of investigations of the children of women who take buprenorphine during pregnancy, including maternal use of illicit drugs, late presentation for prenatal care, infection, poor compliance, poor nutrition, and psychosocial circumstances. Interpretation of data is complicated further by the lack of information on untreated opioid-dependent pregnant women, who would be the most appropriate group for comparison. Rather, women on another form of opioid medication-assisted treatment, or women in the general population are generally used as the comparison group. However, women in these comparison groups may be different from women prescribed buprenorphine-containing products with respect to maternal factors that may lead to poor pregnancy outcomes.

In a multicenter, double-blind, randomized, controlled trial [Maternal Opioid Treatment: Human Experimental Research (MOTHER)] designed primarily to assess neonatal opioid withdrawal effects, opioid-dependent pregnant women were randomized to buprenorphine (n=86) or methadone (n=89) treatment, with enrollment at an average gestational age of 18.7 weeks in both groups. A total of 28 of the 86 women in the buprenorphine group (33%) and 16 of the 89 women in the methadone group (18%) discontinued treatment before the end of pregnancy.

Among women who remained in treatment until delivery, there was no difference between buprenorphine-treated and methadone-treated groups in the number of neonates requiring NOWS treatment or in the peak severity of NOWS. Buprenorphine-exposed neonates required less morphine (mean total dose, 1.1 mg vs. 10.4 mg), had shorter hospital stays (10.0 days vs. 17.5 days), and shorter duration of treatment for NOWS (4.1 days vs. 9.9 days) compared to the methadone-exposed group. There were no differences between groups in other primary outcomes (neonatal head circumference,) or secondary outcomes (weight and length at birth, preterm birth, gestational age at delivery, and 1-minute and 5-minute Apgar scores), or in the rates of maternal or neonatal adverse events. The outcomes among mothers who discontinued treatment before delivery and may have relapsed to illicit opioid use are not known. Because of the imbalance in discontinuation rates between the buprenorphine and methadone groups, the study findings are difficult to interpret.

Animal Data

ZUBSOLV has been shown to have differences in bioavailability compared to other buprenorphine/naloxone-containing sublingual products. The exposure margins listed below are based on body surface area comparisons (mg/m^2) to the human sublingual dose of 16 mg buprenorphine via Suboxone, which is equivalent to a human sublingual dose of 11.4 mg buprenorphine via ZUBSOLV.

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone during the period of organogenesis. Following oral administration to rats, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day (estimated exposure approximately 150 times the human sublingual dose of 16 mg) in the presence of maternal toxicity (mortality). Following oral administration to rabbits, no teratogenic effects were observed at buprenorphine doses up to 40 mg/kg/day (estimated exposure approximately 50 times the human sublingual dose of 16 mg) in the absence of clear maternal toxicity. No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the human sublingual dose of 16 mg). Maternal toxicity resulting in mortality was noted in these studies in both rats and rabbits. Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Maternal toxicity was seen in the high-dose group but not at the lower doses where the findings were observed. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the human sublingual dose of 16 mg). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the human sublingual dose of 16 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the human sublingual dose of 16 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the human sublingual dose of 16 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the human sublingual dose of 16 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the human sublingual dose of 16 mg), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the human daily sublingual dose of 16 mg) in the absence of maternal toxicity or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the human sublingual dose of 16 mg) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the human sublingual dose of 16 mg). No maternal toxicity was noted at doses causing post-implantation loss in this study.

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine from Gestation Day 14 through Lactation Day 21 at 5 mg/kg/day (approximately 3 times the human sublingual dose of 16 mg). Fertility, pre-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the human sublingual dose of 16 mg), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the human sublingual dose of 16 mg), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the human sublingual dose of 16 mg). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the human sublingual dose of 16 mg).

8.2 Lactation

Risk Summary

Based on two studies in 13 lactating women, maintained on buprenorphine treatment, buprenorphine and its metabolite norbuprenorphine were present in low levels in human milk and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is limited. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZUBSOLV and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Clinical Considerations

Advise the breastfeeding women taking buprenorphine products to monitor the infant for increased drowsiness and breathing difficulties.

Data

Data were consistent from two studies (N=13) of breastfeeding infants whose mothers were maintained on sublingual doses of buprenorphine ranging from 2.4 to 24 mg/day, showing that the infants were exposed to less than 1% of the maternal daily dose.

In a study of six lactating women who were taking a median sublingual buprenorphine dose of 0.29 mg/kg/day 5 to 8 days after delivery, breast milk provided a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, equal to 0.2% and 0.12%, respectively, of the maternal weight-adjusted dose (relative dose/kg (%) of norbuprenorphine was calculated from the assumption that buprenorphine and norbuprenorphine are equipotent).

Data from a study of seven lactating women who were taking a median sublingual buprenorphine dose of 7 mg/day an average of 1.12 months after delivery indicated that the mean milk concentrations (C_{avg}) of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the study data, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean absolute infant dose (AID) of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, or a mean relative infant dose (RID) of 0.38% and 0.18%, respectively, of the maternal weight-adjusted dose.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ZUBSOLV have not been established in pediatric patients. This product is not appropriate for the treatment of neonatal opioid withdrawal syndrome in neonates, because it contains naloxone, an opioid antagonist.

8.5 Geriatric Use

Clinical studies of buprenorphine/naloxone sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience have not identified differences in responses between the elderly and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients, the decision to prescribe ZUBSOLV should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone has been evaluated in a pharmacokinetic study. Both drugs are extensively metabolized in the liver. While no clinically significant changes have been observed in subjects with mild hepatic impairment; the plasma levels have been shown to be higher and half-life values have been shown to be longer for both buprenorphine and naloxone in subjects with moderate and severe hepatic impairment. The magnitude of the effects on naloxone is greater than that on buprenorphine in both moderately and severely impaired subjects. The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than in subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment *[see Warnings and Precautions (5.12), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ZUBSOLV contains buprenorphine, a Schedule III substance under the Controlled Substances Act.

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential to be abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The healthcare provider may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Warnings and Precautions (5.7)]*.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy [see Warnings and Precautions (5.5)].

10 OVERDOSAGE

Clinical Presentation

The manifestations of acute buprenorphine overdose include pinpoint pupils, sedation, hypotension, hypoglycemia, respiratory depression, and death.

Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Treatment of Overdose

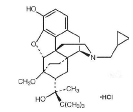
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. An opioid overdose reversal agent may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary. The long duration of action of ZUBSOLV should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose. Insufficient duration of monitoring may put patients at risk.

11 DESCRIPTION

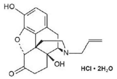
ZUBSOLV (buprenorphine and naloxone) sublingual tablets are white menthol-flavored tablets in an oval shape for the dosage strength 0.7 mg/0.18 mg, a triangular shape for the dosage strength 1.4 mg /0.36 mg, a D shape for the dosage strength 2.9 mg/0.71 mg, a round shape for the dosage strength 5.7 mg/1.4 mg, a diamond shape for the dosage strength 8.6 mg/2.1 mg and a capsule shape for the dosage strength 11.4 mg/2.9 mg. They are debossed with the respective dosage strength of buprenorphine. They contain buprenorphine HCl, an opioid partial agonist and naloxone HCl dihydrate, an opioid antagonist, at a ratio of 4:1 (ratio of free bases). ZUBSOLV is intended for sublingual administration and is available in six dosage strengths, 0.7 mg buprenorphine with 0.18 mg naloxone, 1.4 mg buprenorphine with 0.36 mg naloxone, 2.9 mg buprenorphine with 0.71 mg naloxone, 5.7 mg buprenorphine with 1.4 mg naloxone, 8.6 mg buprenorphine with 2.1 mg naloxone and 11.4 mg buprenorphine with 2.9 mg naloxone. Each sublingual tablet also contains mannitol, citric acid, sodium citrate, microcrystalline cellulose, croscarmellose sodium, sucralose, menthol, silicon dioxide and sodium stearyl fumarate and menthol flavor.

Chemically, buprenorphine HCl is (2S)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4 \cdot HCl$ and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



Naloxone HCl dihydrate has the molecular formula $C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_20$ and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZUBSOLV contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms, if administered parenterally, in individuals physically dependent on full opioid agonists.

12.2 Pharmacodynamics

ZUBSOLV has been shown to have different bioavailability compared to Suboxone tablet. One ZUBSOLV 5.7 mg/1.4 mg tablet provides equivalent buprenorphine exposure and 12% lower naloxone exposure to one Suboxone 8 mg/2 mg tablet. The pharmacodynamic information of other currently marketed buprenorphine/naloxone-containing sublingual products is not directly comparable on a mg basis to ZUBSOLV *[see Dosage and Administration (2.9)]*.

Subjective Effects

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of Suboxone tablets produced opioid agonist effects which reached a maximum between doses of 8 mg/2 mg and 16 mg/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1 mg, 2 mg, 4 mg, 8 mg, 16 mg, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8 mg-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects

Buprenorphine in IV (2 mg, 4 mg, 8 mg, 12 mg and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1 mg, 2 mg, 4 mg, 8 mg, 16 mg, or 32 mg) and oral methadone (15 mg, 30 mg, 45 mg, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and Suboxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation *[see Adverse Reactions (6.2)]*.

Cardiac Electrophysiology

Thorough QT studies with buprenorphine products have demonstrated QT prolongation ≤15 msec.

12.3 Pharmacokinetics

Absorption

Plasma levels of buprenorphine and naloxone increased with the sublingual dose of ZUBSOLV. There was wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased with the increase in dose (in the range of 1.4 mg to 11.4 mg), although the increase was not directly dose-proportional. Naloxone did not affect the pharmacokinetics of buprenorphine.

ZUBSOLV has been shown to have different bioavailability compared to Suboxone tablet. One ZUBSOLV 5.7 mg/1.4 mg tablet provides equivalent buprenorphine exposure and 12% lower naloxone exposure to one Suboxone 8 mg/2 mg tablet.

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Elimination Metabolism

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in-vitro; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Excretion

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

When ZUBSOLV tablets are administered sublingually, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug Interaction Studies

CYP3A4 Inhibitors and Inducers

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in-vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns *[see Drug Interactions (7)]*.

Specific Populations

Hepatic Impairment

In a pharmacokinetic study, the disposition of buprenorphine and naloxone were determined after administering a Suboxone 2.0 mg/0.5 mg (buprenorphine/naloxone) sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine and naloxone in patients with hepatic impairment were compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean C_{max}, $AUC_{0\text{-}last}$, and half-life values of both buprenorphine and naloxone were not clinically significant. No dosing adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean C_{max}, $AUC_{0\text{-}last}$, and half-life values of both buprenorphine and naloxone were increased; the effects on naloxone are greater than that on buprenorphine (Table 5).

Table 5. Changes in Pharmacokinetic Parameters in Subjects with Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects	Increase in naloxone compared to healthy subjects
Moderate	C_{max}	8%	170%
	$AUC_{0\text{-}last}$	64%	218%
	Half-life	35%	165%
Severe	C_{max}	72%	1030%
	$AUC_{0\text{-}last}$	181%	1302%
	Half-life	57%	122%

The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than subjects with moderate hepatic impairment *[see Warnings and Precautions (5.12) and Use in Specific Populations 8.6)]*.

HCV infection

In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-}last}$, and half-life values of buprenorphine and naloxone were not clinically significant in comparison to healthy subjects without HCV infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ZUBSOLV has been shown to have differences in bioavailability compared to other buprenorphine/naloxone-containing sublingual products. The exposure margins listed below are based on body surface area comparisons (mg/m^2) to the recommended human sublingual dose of 16 mg buprenorphine via Suboxone, which is equivalent to a human sublingual dose of 11.4 mg buprenorphine via ZUBSOLV.

Carcinogenicity

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7 mg/kg/day, 31 mg/kg/day, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6 mg/kg/day, 5.5 mg/kg/day, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human sublingual dose) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human sublingual dose).

Mutagenicity

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of S. typhimurium and two strains of E. coli. The combination was not clastogenic in an in vitro cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (S. cerevisiae) for recombinant, gene convertant, or forward mutations; negative in Bacillus subtilis "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (E. coli) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human sublingual dose) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human sublingual dose) had no adverse effect on fertility.

14 CLINICAL STUDIES

The induction of buprenorphine therapy with ZUBSOLV was evaluated in two blinded randomized, non-inferiority studies. The identical blinded induction phase component of the studies was designed to assess the tolerability of ZUBSOLV versus generic buprenorphine tablets when used as initial treatment, as measured by retention in treatment. The studies included opioid dependent (DSM-IV criteria) male and female patients 18 to 65 years of age. Induction doses for generic buprenorphine tablets were 8 mg for day 1 and 8 mg or 16 mg for day 2. The induction doses for ZUBSOLV were 5.7 mg/1.4 mg for day 1 and 5.7 mg/1.4 mg or 11.4 mg/2.8 mg for day 2. In the first study, 758 patients were randomized. In the second study, 310 patients were randomized.

Both protocols stipulated that first Day 1 dose would be given under supervision, with an initial dose of buprenorphine 2 mg or ZUBSOLV 1.4 mg. Subsequently, investigators were provided an option to give buprenorphine 6 mg or ZUBSOLV 4.2 mg as a single dose 1.5 hours after the second dose, or to divide the second dose of study medication into 3 separate dosing occasions of ZUBSOLV 1.4 mg/0.36 mg or generic buprenorphine 2 mg each, 1 to 2 hours between doses, if there was precipitated withdrawal after the first dose, as assessed by the investigator. The option to divide the second dose was used at the discretion of the investigators only rarely in Study 2 (5%), compared to more frequent use in Study 1 (22%).

Results for Day 3 retention rate from each study are presented in Table 6. The lower rate of retention on Day 3 observed for ZUBSOLV in comparison to generic buprenorphine in Study 2 may be attributable to the infrequent use of divided dosing.

Table 6. Retention at Day 3 (full analysis set)

Study 1			
Number in population	**ZUBSOLV (N=383)**	**Generic BUP (N=375)**	**Overall (N=758)**
Retention at Day 3	357 (93%)	344 (92%)	701 (93%)
Study 2			
Number in population	**ZUBSOLV (N=155)**	**Generic BUP (N=155)**	**Overall (N=310)**
Retention at Day 3	132 (85%)	147 (95%)	279 (90%)

16 HOW SUPPLIED / STORAGE AND HANDLING

ZUBSOLV sublingual tablets are menthol-flavored white tablets supplied in aluminum/aluminum child resistant unit dose blister packages. ZUBSOLV is available in six dosage strengths imprinted in their respective buprenorphine strength

- Buprenorphine 0.7 mg /naloxone 0.18 mg, oval shape, imprinted with ".7"
- Buprenorphine 1.4 mg /naloxone 0.36 mg, triangular shape, imprinted with "1.4"
- Buprenorphine 2.9 mg /naloxone 0.71mg, D shape, imprinted with "2.9"
- Buprenorphine 5.7 mg /naloxone 1.4 mg, round shape, imprinted with "5.7"
- Buprenorphine 8.6 mg /naloxone 2.1 mg, diamond shape, imprinted with "8.6"
- Buprenorphine 11.4 mg /naloxone 2.9 mg, capsule shape, imprinted with "11.4"

- NDC 82111-201-30 (buprenorphine 0.7 mg /naloxone 0.18 mg) sublingual tablet – 3x10 tablets per carton
- NDC 82111-202-30 (buprenorphine 1.4 mg /naloxone 0.36 mg) sublingual tablet – 3x10 tablets per carton
- NDC 82111-203-30 (buprenorphine 2.9 mg /naloxone 0.71 mg) sublingual tablet – 3x10 tablets per carton
- NDC 82111-204-30 (buprenorphine 5.7 mg /naloxone 1.4 mg) sublingual tablet – 3x10 tablets per carton
- NDC 82111-205-30 (buprenorphine 8.6 mg /naloxone 2.1 mg) sublingual tablet – 3x10 tablets per carton
- NDC 82111-206-30 (buprenorphine 11.4 mg /naloxone 2.9 mg) sublingual tablet – 3x10 tablets per carton

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) *[see USP Controlled Room Temperature]*

Store ZUBSOLV securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store ZUBSOLV securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.11), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving ZUBSOLV unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused ZUBSOLV should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Advise patients to read the FDA-approved patient labeling. (Medication Guide)

Safe Use

Before initiating treatment with ZUBSOLV, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time ZUBSOLV is dispensed because new information may be available.

- ZUBSOLV must be administered whole. Advise patients not to cut, chew, or swallow ZUBSOLV.
- Inform patients and caregivers that potentially fatal additive effects may occur if ZUBSOLV is used with benzodiazepines or other CNS depressants (e.g., alcohol, non-benzodiazepines, sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids) and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.2, 5.3), Drug Interactions (7)]*.
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.2)]*.
- Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene) and discuss the importance of having access to an opioid overdose reversal agent. Because patients being treated for opioid use disorder are at risk for relapse, discuss the importance of having access to an opioid overdose reversal agent. Also discuss the importance of having access to an opioid overdose reversal agent if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter (some products), or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

There are important differences among the opioid overdose reversal agents. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Educate patients and caregivers on how to recognize the signs and symptoms of an opioid overdose.

Explain to patients and caregivers that effects of opioid overdose reversal agents like naloxone and nalmefene are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if an opioid overdose reversal agent is administered. Repeat administration may be necessary, particularly for overdose involving buprenorphine *[Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.

Advise patients and caregivers:

  - how to treat with an opioid overdose reversal agent in the event of an opioid overdose
  - to tell family and friends about their opioid overdose reversal agent, and to keep it in a place where family and friends can easily access it in an emergency
  - to read the Patient Information (or other educational material) that will come with their opioid overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.
- Advise patients that ZUBSOLV contain an opioid that can be a target for people who abuse prescription medications or street drugs, to keep their tablets in a safe place, and to protect them from theft.
- Instruct patients to keep ZUBSOLV in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Advise patients to seek medical attention immediately if a child is exposed to ZUBSOLV.
- Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.
- Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.6)]*.
- Advise patients to never give ZUBSOLV to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away this medication is against the law.
- Advise patients that, after ZUBSOLV has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking ZUBSOLV before brushing teeth *[see Warnings and Precautions (5.13)]*.
- Refer patients to dental care services and encourage them to have regular dental checkups while taking ZUBSOLV. Instruct patients to inform their dentist that they have started therapy on ZUBSOLV *[see Warnings and Precautions (5.13)]*.
- Caution patients that ZUBSOLV may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.15)]*.
- Advise patients not to change the dosage of ZUBSOLV without consulting their healthcare provider.
- Advise patients to take ZUBSOLV once a day, after induction.
- Advise patients that if they miss a dose of ZUBSOLV they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at the regular time.
- Inform patients that ZUBSOLV can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Advise patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their healthcare provider on a tapering schedule and inform them of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Advise patients that, like other opioids, ZUBSOLV may produce orthostatic hypotension in ambulatory individuals *[see Warnings and Precautions. (5.16)]*.
- Advise patients to inform their healthcare provider if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used *[see Drug Interactions (7)]*.
- Advise women that if they are pregnant while being treated with ZUBSOLV, the baby may have signs of withdrawal at birth and that withdrawal is treatable *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.
- Advise women who are breastfeeding to monitor the infant for drowsiness and difficulty breathing *[see Use in Specific Populations (8.2)]*.
- Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.
- Advise patients to inform their family members that, in the event of emergency, the treating healthcare provider or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with ZUBSOLV.

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