PRODUCT MONOGRAPH

[N]ACT BUPRENORPHINE/NALOXONE

buprenorphine (as buprenorphine hydrochloride)
and
naloxone (as naloxone hydrochloride dihydrate)

Sublingual Tablets 2 mg/0.5 mg and 8 mg/2 mg

Partial Opiate Agonist
and
Opiate Antagonist

Actavis Pharma Company
6733 Mississauga Road, Suite 400
Mississauga, Ontario
L5N6J5

Date of Revision:
March 7, 2017

Control No.: 203010

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Non-Medicinal Ingredients
sublingual	sublingual tablets • 2 mg buprenorphine/0.5 mg naloxone • 8 mg buprenorphine/ 2 mg naloxone	citric acid, crospovidone, lactose monohydrate, magnesium stearate, mannitol, natural & artificial lemon flavor, povidone, pregelatinized starch, sodium citrate and sucralose

INDICATIONS AND CLINICAL USE

Adults
ACT BUPRENORPHINE/NALOXONE (buprenorphine and naloxone) is indicated for substitution treatment in adults with problematic opioid drug dependence.

Geriatrics (>65 years of age)

The safety and efficacy of buprenorphine and naloxone have not been established in adults over 65 years of age. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, respiratory or cardiac function, concomitant disease or other drug therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (<18 years of age)

The safety and efficacy of buprenorphine and naloxone in patients below the age of 18 years have not been established, therefore ACT BUPRENORPHINE/NALOXONE is not recommended in this patient population.

Physician Prescribing Information
Patients prescribed ACT BUPRENORPHINE/NALOXONE should be carefully monitored within a framework of medical, social, and psychological support as part of a comprehensive opioid dependence treatment program.

ACT BUPRENORPHINE/NALOXONE sublingual tablets should only be prescribed by physicians who meet the following requirements:

i) Experience in substitution treatment in opioid drug dependence, and
ii) Completion of a recognized Buprenorphine and Naloxone Education Program.

The Buprenorphine and Naloxone Education Program is a risk management program that is founded on the following four core components that provide for the safe and effective use of the drug within a framework of medical, social and psychological support:
- training of the prescribing physicians in the use of Buprenorphine and Naloxone sublingual tablets;
- maintenance of a list of Buprenorphine and Naloxone Education Program trained physicians;
- daily dosing supervised by a healthcare professional, progressing to unsupervised administration as the patient's clinical stability permits;
- take-home doses once the patient has sufficient clinical stability and is able to safely store ACT BUPRENORPHINE/NALOXONE. Take-home doses should be assessed and reviewed on a regular basis.

Physicians may obtain more information about the Buprenorphine and Naloxone Education Program by calling the following toll-free phone number: 1-866-254-6111.

CONTRAINDICATIONS

ACT BUPRENORPHINE/NALOXONE sublingual tablet is contraindicated in

- Patients who are hypersensitive to buprenorphine, naloxone, or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Opioid naive patients.
- Patients with severe respiratory insufficiency: e.g., acute or severe bronchial asthma, chronic obstructive airway, status asthmaticus, acute respiratory depression and/or cor pulmonale.
- Patients with severe hepatic impairment.
- Patients with acute alcoholism, delirium tremens and convulsive disorders. Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis). Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

<u>Limitations of Use</u>
ACT BUPRENORPHINE/NALOXONE must be dispensed daily under the supervision of a healthcare professional, until the patient has sufficient clinical stability and is able to safely

store ACT BUPRENORPHINE/NALOXONE take-home doses (see DOSAGE AND ADMINISTRATION).

Appropriate security measures should be taken to safeguard stocks of ACT BUPRENORPHINE/NALOXONE against diversion.

Addiction, Abuse, and Misuse

Abuse and diversion of buprenorphine, a component of buprenorphine and naloxone, and of buprenorphine and naloxone itself, have been reported. All patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS).

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with the use of ACT BUPRENORPHINE/NALOXONE. Patients should be monitored for respiratory depression, especially during initiation of ACT BUPRENORPHINE/NALOXONE or following a dose increase.

ACT BUPRENORPHINE/NALOXONE sublingual tablets should be placed under the tongue until dissolved. Cutting, breaking, crushing, or chewing ACT BUPRENORPHINE/NALOXONE can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Accidental Exposure

Accidental ingestion of even one dose of ACT BUPRENORPHINE/NALOXONE by individuals not physically dependent on opioids, especially children, can result in a fatal overdose of buprenorphine (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of ACT BUPRENORPHINE/NALOXONE during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol

The co-ingestion of alcohol with ACT BUPRENORPHINE/NALOXONE should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks from concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of ACT BUPRENORPHINE/NALOXONE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**

- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General

ACT BUPRENORPHINE/NALOXONE sublingual tablets are indicated for substitution treatment in adults with problematic opioid drug dependence, and as with other opioid substitution medications, should be used within the framework of medical, social and psychological support as part of a comprehensive opioid dependence treatment program.

Abuse and Misuse Potential

ACT BUPRENORPHINE/NALOXONE can be misused or abused in a manner similar to other opioids, legal or illicit, which can lead to overdose and death. ACT BUPRENORPHINE/NALOXONE is intended for sublingual use only. The tablets should be allowed to dissolve under the tongue and not chewed or crushed.

Prescribe and dispense ACT BUPRENORPHINE/NALOXONE with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the patient's home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment and should be given only with appropriate patient follow-up visits.

Sub-optimal treatment with ACT BUPRENORPHINE/NALOXONE may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with ACT BUPRENORPHINE/NALOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or sedative-hypnotics such as benzodiazepines.

The combining of buprenorphine with naloxone in ACT BUPRENORPHINE/NALOXONE is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of ACT BUPRENORPHINE/NALOXONE is expected to be less likely than with buprenorphine alone since the naloxone in ACT BUPRENORPHINE/NALOXONE can precipitate withdrawal in individuals dependent on heroin, methadone, or other opioid agonists.

Some risks of misuse and abuse include overdose, respiratory depression and hepatic injury, and spread of blood borne viral infections.

Extra precautions are required in patients dependent upon concomitant CNS-active substances, including alcohol, and patients with sporadic use of concomitant non-opioid medications (see DOSAGE AND ADMINISTRATION).

Carcinogenesis and Mutagenesis

See **TOXICOLOGY** section.

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS**, **Post- Marketing Experience**).

Cardiovascular

ACT BUPRENORPHINE/NALOXONE may cause orthostatic hypotension in ambulatory patients.

ACT BUPRENORPHINE/NALOXONE administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines, and other tranquilizers, sedatives/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of ACT BUPRENORPHINE/NALOXONE.

The use of ACT BUPRENORPHINE/NALOXONE in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence

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.

Buprenorphine can be abused in a manner similar to other opioids. 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.

Abrupt discontinuation of treatment is not recommended as it may result in an opioid withdrawal syndrome that may be delayed in onset. Signs and symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, <Adjustment or Reduction of Dosage>).

Gastrointestinal Effects

Buprenorphine, a component of ACT BUPRENORPHINE/NALOXONE, and other morphine-like opioids have been shown to decrease bowel motility and increase intracholedochal pressure. ACT BUPRENORPHINE/NALOXONE may obscure the diagnosis or clinical course of patients with acute abdominal conditions, and should be administered with caution to patients with dysfunction of the biliary tract.

Neonatal Opioid Withdrawal Syndrome (NOWS)

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 the opioid withdrawal syndrome in adults, the NOWS may be life-threatening if not recognized and treated in the neonate.

NOWS may present 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. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to minimize the risk of respiratory depression or withdrawal syndrome in neonates.

Advise pregnant women receiving opioid addiction treatment with ACT BUPRENORPHINE/NALOXONE of the risk of a NOWS and ensure that appropriate treatment will be available.

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.

Neurologic Effects

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Buprenorphine should be used with caution and in a reduced dosage during concomitant administration of other opioids, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioids (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when ACT BUPRENORPHINE/NALOXONE is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been

determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

ACT BUPRENORPHINE/NALOXONE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation,** and **DRUG INTERACTIONS**).

Serotonin Syndrome:

ACT BUPRENORPHINE/NALOXONE could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. ACT BUPRENORPHINE/NALOXONE should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with a history of seizure, head injury, intracranial lesions, and other circumstances when cerebrospinal fluid pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness, or changes in the perception of pain as a symptom of disease and may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease. As buprenorphine is an opioid, pain as a symptom of disease may be attenuated.

Peri-Operative Considerations

ACT BUPRENORPHINE/NALOXONE is not indicated for the treatment of pain. For patients that may require pain management in the post-operative period, please see DRUG INTERACTIONS, opioid analgesic.)

Impairment of Ability to Drive or Operate Machinery

ACT BUPRENORPHINE/NALOXONE may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery.

Patients should be cautioned about operating hazardous machinery and automobiles, until they are reasonably certain that ACT BUPRENORPHINE/NALOXONE therapy does not adversely affect their ability to engage in such activities.

ACT BUPRENORPHINE/NALOXONE may cause orthostatic hypotension, drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used together

with alcohol or central nervous system depressants (such as benzodiazepines, tranquilizers, sedatives or hypnotics), the effect is likely to be more pronounced.

Respiratory

Respiratory Depression

Clinically significant respiratory depression and death may occur in patients receiving buprenorphine and naloxone. Some cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines, when high dose buprenorphine was administered to individuals not physically dependent on opioids, or with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with ACT BUPRENORPHINE/NALOXONE, particularly when ACT BUPRENORPHINE/NALOXONE is misused or abused.

ACT BUPRENORPHINE/NALOXONE may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure and access (see SPECIAL HANDLING INSTRUCTIONS).

ACT BUPRENORPHINE/NALOXONE should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression, or kyphoscoliosis), in the elderly and in debilitated patients. Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered.

In the case of overdose, primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, as required. In patients with respiratory depression, symptomatic treatment following standard intensive care measures should be instituted (see OVERDOSAGE).

Hepatic Effects

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 hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. 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 injection 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 are 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, ACT BUPRENORPHINE/NALOXONE 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.

Immune

Allergic Reactions

Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, urticaria, and pruritus. Cases of bronchospasm, angioedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone or any component of the formulation is a contraindication to buprenorphine and naloxone use.

Precipitation of opioid withdrawal syndrome

Because of the partial agonist properties of buprenorphine, ACT BUPRENORPHINE/NALOXONE can precipitate withdrawal symptoms in opioid-dependent patients if administered before the agonist effects resulting from recent opioid use or misuse have subsided. Because it contains naloxone, ACT BUPRENORPHINE/NALOXONE may produce marked and intense withdrawal signs and symptoms if misused or abused intranasally or by injection by individuals dependent on full opioid agonists such as heroin, morphine or methadone.

To avoid precipitating an opioid withdrawal syndrome during induction onto ACT BUPRENORPHINE/NALOXONE from short-acting or long-acting opioids, the patient should show objective signs and symptoms of at least moderate withdrawal prior to induction dosing. For example, a moderate score of withdrawal, equal or greater than 13 on the Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment.

General Precautions

As with other opioids, ACT BUPRENORPHINE/NALOXONE should be used with caution in patients with the following conditions:

- myxedema, hypothyroidism, or adrenal insufficiency (e.g. Addison's disease);
- toxic psychoses;
- hypotension, prostatic hypertrophy or urethral stricture.

Opioid-induced miosis, changes in the level of consciousness, or changes in the perception of pain as a symptom of disease, may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease. Opioids should be administered with caution to elderly or debilitated patients.

Pregnant Women

There are no adequate and well-controlled studies of buprenorphine and naloxone use in pregnant women; therefore, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

NOWS may occur in newborn infants of mothers who are receiving treatment with ACT BUPRENORPHINE/NALOXONE.

NOWS may present 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 NOWS may vary. Observe newborns for signs of NOWS and manage accordingly.

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited published data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy have not shown an increased risk of major malformations. Based on these studies the incidence of NOWS is not clear and there does not appear to be a dose-response relationship.

Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses. Pre-and postnatal development studies in rats demonstrated dystocia, increased neonatal deaths, and developmental delays. No clear teratogenic effects were seen with a range of doses equivalent to or greater than the human dose. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related. Embryo-fetal death was also observed in both rats and rabbits.

Labor and Delivery

As with all opioids, use of buprenorphine prior to delivery may result in respiratory depression in the newborn. Closely monitor neonates for signs of respiratory depression. An opioid antagonist such as naloxone should be available for reversal of opioid induced respiratory depression in the neonate.

Nursing Women

Buprenorphine and its metabolite norbuprenorphine have been found in low levels in human milk and infant urine. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is minimal. Caution should be exercised when ACT BUPRENORPHINE/NALOXONE is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for buprenorphine and naloxone, and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Limited data from published literature have not reported adverse reactions in breastfed infants exposed to buprenorphine through breast milk, however nursing mothers taking ACT BUPRENORPHINE/NALOXONE should be advised to monitor the infant for increased drowsiness and breathing difficulties and infants should be regularly monitored by a health care professional.

Pediatrics (< 18 years of age)

ACT BUPRENORPHINE/NALOXONE is not recommended for use in patients below the age of 18

years. The safety and efficacy of buprenorphine and naloxone in children have not been established.

Geriatrics (> 65 years)

The safety and efficacy of buprenorphine and naloxone in elderly patients over 65 years of age have not been established.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrating upwards slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Patients with Hepatic Impairment:

ACT BUPRENORPHINE/NALOXONE is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. If ACT BUPRENORPHINE/NALOXONE is used in this patient population, caution is advised (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Both buprenorphine and naloxone are extensively metabolized by the liver. In patients with moderate and severe hepatic impairment, plasma levels and half-life values of both buprenorphine and naloxone were found to be markedly increased compared to healthy subjects. This effect was more pronounced in patients with severe hepatic impairment.

Hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, and the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. 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. Dose adjustments may be considered in cases of mild to moderate hepatic impairment, and patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and / or buprenorphine.

As with other opioids, buprenorphine has been shown to increase intracholedochal pressure and should therefore be administered with caution to patients with dysfunction of the biliary tract.

Patients with Renal Impairment:

Renal elimination plays a relatively minor role (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency) in the overall clearance of buprenorphine; therefore, dose modification based on renal function is generally not required. However, metabolites of buprenorphine accumulate in patients with advanced renal failure. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} <30 ml/min) which may require dose adjustment.

The effects of renal failure on naloxone pharmacokinetics are unknown.

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following long term 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.

Monitoring and Laboratory Tests

Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Regular monitoring of liver function is recommended. Patients who are positive for viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at greater risk of liver injury.

Information for Patients

- Patients should be advised to keep ACT BUPRENORPHINE/NALOXONE out of reach and sight of children to prevent accidental ingestion that can result in death. Patients should be advised not to take this medicine in front of children. Patients should be advised that if a child is exposed to ACT BUPRENORPHINE/NALOXONE sublingual tablets, medical attention should be sought immediately.
- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines, sedatives, tranquilizers, antidepressants or alcohol while taking ACT BUPRENORPHINE/NALOXONE, which may result in serious harm or death. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician.
- Patients should inform their physician if other prescription medications are currently being used or are prescribed for future use.
- Patients should be cautioned to keep their tablets in a safe place, and to protect them from theft. Patients should be advised never to give ACT BUPRENORPHINE/NALOXONE sublingual tablets to anyone else, as it may cause harm or death. Selling or giving away this medicine is against the law.
- Patients should inform their family members that, in the event of overdose, the treating physician or emergency staff should be informed that the patient is physically dependent on narcotics and is being treated with ACT BUPRENORPHINE/NALOXONE.
- Patients should be cautioned about driving a car or operating hazardous machinery, including automobiles, until they are reasonably certain that ACT BUPRENORPHINE/NALOXONE therapy does not adversely affect their ability to engage in such activities. ACT BUPRENORPHINE/NALOXONE may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery, especially during drug induction and dose adjustment.

- Patients should be cautioned that, like other opioids, ACT BUPRENORPHINE/NALOXONE may cause orthostatic hypotension in ambulatory individuals.
- Patients should be advised to take ACT BUPRENORPHINE/NALOXONE sublingual tablets once a day. Patients should be advised not to change the dosage of ACT BUPRENORPHINE/NALOXONE sublingual tablets without consulting their physician.
- Patients should be informed that ACT BUPRENORPHINE/NALOXONE sublingual tablets can cause opioid drug dependence and that opioid withdrawal signs and symptoms may occur when the medication is discontinued. Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse.
- Women of childbearing potential, who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using ACT BUPRENORPHINE/NALOXONE sublingual tablets during pregnancy. Patients who are breastfeeding should be warned to monitor the infant for drowsiness and difficulty breathing.
- Athletes should be aware that this medicine may cause a positive reaction to "anti-doping tests" and should inform the authorities that they are being treated with ACT BUPRENORPHINE/ NALOXONE.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinically significant respiratory depression and death may occur in patients receiving ACT BUPRENORPHINE/ NALOXONE, particularly when used in combination with benzodiazepines and other CNS depressants such as other opioids or alcohol (see WARNINGS AND PRECAUTIONS).

The most commonly reported treatment related adverse reactions reported during the pivotal clinical studies were headache, and signs and symptoms commonly associated with drug withdrawal (i.e. abdominal pain, anxiety, diarrhoea, muscle aches, insomnia, headache, constipation, nausea and hyperhidrosis). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

In patients with marked opioid dependence, initial administration of ACT BUPRENORPHINE/ NALOXONE can produce a withdrawal effect similar to that associated with naloxone.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the pivotal clinical study (CR96/013 [double-blind] + CR96/014 [open label extension]), of 472 patients treated with sublingual tablets containing buprenorphine in combination with naloxone, 334 patients were treated for 3 months, 261 patients were treated for greater than 6 months and 100

patients were treated up to one year. The most used dose was 16 mg/day. Treatment-emergent adverse events reported in the pivotal clinical study of buprenorphine and naloxone (≥1.0 % of buprenorphine and naloxone-treated patients) are listed in Table 1.

Table 1 - Treatment-emergent adverse events reported in the pivotal clinical study of buprenorphine and naloxone (≥1.0 % of buprenorphine and naloxone -treated patients)

	Buprenorphine and naloxone N = 472
Body as a Whole	
Headache	202 (42.8%)
Pain	197 (41.7%)
Withdrawal Syndrome	194 (41.1%)
Infection	149 (31.6%)
Pain Back	132 (28.0%)
Flu Syndrome	89 (18.9%)
Pain Abdominal	77 (16.3%)
Injury Accidental	72 (15.3%)
Asthenia	48 (10.2 %)
Chills	44 (9.3%)
Fever	36 (7.6%)
Pain Chest	23 (4.9%)
Abscess	17 (3.6%)
Pain Neck	12 (2.5%)
Malaise	9 (1.9%)
Allergic Reaction	8 (1.7%)
Edema Face	8 (1.7%)
Cyst	7 (1.5%)
Infection Viral	5 (1.1%)
Neck Rigid	5 (1.1%)
Cardiovascular System	
Vasodilation	29 (6.1%)
Hypertension	17 (3.6%)
Migraine	13 (2.8%)
Digestive System	
Constipation	115 (24.4%)
Nausea	76 (16.1%)
Vomiting	61 (12.9%)
Dyspepsia	45 (9.5%)
Diarrhea	50 (10.6%)
Tooth Disorder	37 (7.8%)
Liver Function Abnormal	18 (3.8%)
Anorexia	16 (3.4%)
Nausea/Vomiting	13 (2.8%)
Flatulence	11 (2.3%)
Abscess Periodontal	10 (2.1%)
Gastrointestinal Disorder	7 (1.5%)
Ulcer Mouth	6 (1.3%)
Stomatitis	5 (1.1%)

Table 1 - Treatment-emergent adverse events reported in the pivotal clinical study of buprenorphine and naloxone (≥1.0 % of buprenorphine and naloxone -treated patients)

	Buprenorphine and naloxone N = 472
Hemic and Lymphatic System	
Anemia	7 (1.5%)
Ecchymosis	6 (1.3%)
Lymphadenopathy	5 (1.1%)
Metabolism and Nutritional Disorders	
Peripheral Edema	24 (5.1%)
Weight Decreased	15 (3.2%)
Hyperglycemia	5 (1.1%)
Musculoskeletal System	
Myalgia	31 (6.6%)
Arthralgia	20 (4.2%)
Leg Cramps	13 (2.8%)
Joint Disorder	9 (1.9%)
Arthritis	5 (1.1%)
Nervous System	
Insomnia	138 (29.2%)
Depression	70 (14.8%)
Anxiety	65 (13.8%)
Nervousness	42 (8.9%)
Somnolence	40 (8.5%)
Dizziness	33 (7.0%)
Paresthesia	28 (5.9%)
Agitation	10 (2.1%)
Dream Abnormal	9 (1.9%)
Drug Dependence	9 (1.9%)
Hypertonia	9 (1.9%)
Libido Decreased	9 (1.9%)
Tremor	7 (1.5%)
Thinking Abnormal	6 (1.3%)
Respiratory System	
Rhinitis	75 (15.9%)
Pharyngitis	64 (13.6%)
Cough Increased	36 (7.6%)
Asthma	21 (4.4%)
Pneumonia	12 (2.5%)
Lung Disorder	10 (2.1%)
Bronchitis	9 (1.9%)
Dyspnea	9 (1.9%)
Respiratory Disorder	7 (1.5%)
Sinusitis	7 (1.5%)
Sputum Increased	5 (1.1%)
Yawning	6 (1.3%)

Table 1 - Treatment-emergent adverse events reported in the pivotal clinical study of buprenorphine and naloxone (≥1.0 % of buprenorphine and naloxone -treated patients)

	Buprenorphine and naloxone N = 472
Skin and Appendages	
Sweating	74 (15.7%)
Rash	23 (4.9%)
Pruritus	11 (2.3%)
Dry Skin	6 (1.3%)
Herpes Simplex	6 (1.3%)
Nodule Skin	6 (1.3%)
Urticaria	6 (1.3%)
Acne	5 (1.1%)
Contact Dermatitis	5 (1.1%)
Special Senses	
Conjunctivitis	14 (3.0%)
Lacrimation Disorder	14 (3.0%)
Eye Disorder	8 (1.7%)
Pain Ear	8 (1.7%)
Amblyopia	5 (1.1%)
Urogenital System	
Dysmenorrhea	19 (4.0%)
Urinary Tract Infection	19 (4.0%)
Urine Abnormal	12 (2.5%)
Impotence	11 (2.3%)
Vaginitis	11 (2.3%)
Dysuria	9 (1.9%)
Hematuria	8 (1.7%)

The most commonly observed adverse reactions in this study are consistent with opioid withdrawal or agonist effects. Although it is not possible to compare adverse effects across trials because of differences in methodology and patient populations, the undesirable effects observed in other studies are qualitatively similar.

Nausea: Nausea is a common side effect with opioids and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Treatment-emergent adverse reactions reported as less common (<1%) in the pivotal buprenorphine and naloxone clinical studies included:

Body as a Whole: carcinoma, cellulitis, chills/fever, hangover, heat stroke, hernia, human immunodeficiency virus (HIV) test positive, hostility, hypothermia, infection fungal, infection parasitic, neoplasia, overdose, pain chest (substernal), pain flank, pain pelvic, photosensitivity, pain rib and suicide attempt.

Cardiovascular System: angina pectoris, bradycardia, electrocardiogram abnormal, hypotension, myocardial infarction, palpitation, phlebitis, tachycardia, thrombosis, thrombophlebitis (deep), vascular disorder and varicose vein.

Digestive System: appetite increased, colitis, dry mouth, dysphagia, eructation, gastritis, gamma glutamyl transpeptidase increased, gingivitis, glossitis, gum hemorrhage, rectal hemorrhage, hematemesis, hepatitis C, rectal disorder, saliva increased, stomatitis/ulcer, tenesmus, tooth caries, ulcer peptic, stomach ulcer hemorrhage and tongue discolouration.

Endocrine System: sexual function abnormal.

Hemic and Lymphatic System: leucocytosis, leucopenia, methemoglobin, thrombocythemia, thrombocytopenia and white blood cells abnormal.

Metabolism and Nutritional Disorders: alanine aminotransferase increased, albuminuria, alkaline phosphatase increased, aspartate aminotransferase increased, blood urea nitrogen increased, creatinine increased, edema, electrolytes abnormal, hypercholesterolemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased, weight increased.

Musculoskeletal System: bursitis, myasthenia, pain bone, spasm general, tendon disorder and tenosynovitis.

Nervous System: amnesia, apathy, convulsion, depersonalization, emotional lability, euphoric mood, hallucination, hyperkinesia, miosis, neuralgia, neuropathy, paralysis facial, speech disorder, stupor, twitch, urinary retention and vertigo.

Respiratory System: emphysema, epistaxis, hemoptysis, hiccup, laryngitis, pleural disorder and voice alteration.

Skin and Appendages: alopecia, exfoliative dermatitis, fungus dermatitis, hair disorder, lichen dermatitis, melanoma skin, neoplasia skin, psoriasis, rash maculopapular, rash vesiculobullous, skin disorder and ulcer skin.

Special Senses: corneal lesion, deafness, ear disorder, otitis media, pain eye, tinnitus.

Urogenital System: amenorrhea, ejaculation abnormal, fibrocystic breast, leukorrhea, mastitis, menorrhagia, menstrual disorder, metrorrhagia, neoplasia breast, nephrolithiasis, orchitis, pain breast, pain kidney, papanikolaou smear suspicious, unintended pregnancy, prostate disorder,

salpingitis, testis disorder, urethritis, urination impaired, urinary frequency, and urinary urgency.

Buprenorphine used alone

Buprenorphine used alone for treatment of opioid dependence has been associated with the following signs and symptoms (> 1 %): constipation, headache, insomnia, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension, and sweating. Other adverse events (< 0.1 %) have been reported in association with buprenorphine alone. These are:

- respiratory depression (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS);
- hepatic necrosis and hepatitis (see WARNINGS AND PRECAUTIONS); and
- hallucinations.

Cases of bronchospasm, angioneurotic edema and anaphylactic shock have also been reported.

In cases of drug abuse or intentional drug misuse, some adverse experiences attributed to the act of misuse rather than the medicinal product have included: local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis, and other serious infections (see WARNINGS AND PRECAUTIONS).

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

NOWS has been reported among newborns of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that from short acting full mu-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see WARNINGS AND PRECAUTIONS).

Post-marketing Experience

Table 2 lists adverse drug reactions reported during post-marketing surveillance, not reported elsewhere in the label, some of which may have only been observed with buprenorphine alone in the treatment of opioid dependence. Adverse drug reactions are presented by MedDRA System Organ Class in order by preferred term.

Table 2 - Adverse Drug Reactions Collected Through Post-marketing Surveillance

System Organ Class	Preferred Term
Hepatobiliary disorders	Cytolytic hepatitis Hepatorenal syndrome Jaundice
Investigations	Transaminases increased
Nervous system disorders	Hepatic encephalopathy Syncope

Androgen deficiency: 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.

DRUG INTERACTIONS

Serious Drug Interactions

Patients taking ACT BUPRENORPHINE/NALOXONE together with alcohol or other CNS depressants may exhibit signs of increased CNS depression, e.g. respiratory depression, hypotension, profound sedation, coma or death.

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants:

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). ACT BUPRENORPHINE/NALOXONE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

The use of alcohol while taking ACT BUPRENORPHINE/NALOXONE should be avoided.

Alcohol
Alcohol increases the sedative effect of opioids. Alcoholic beverages should be avoided while taking ACT BUPRENORPHINE/ NALOXONE. Medication containing alcohol should be co-administered with caution (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box).

ACT BUPRENORPHINE/NALOXONE should be used cautiously when co-administered with:

Benzodiazepines
This combination may result in death due to respiratory depression of central origin, therefore patients should be closely monitored when prescribed this combination. This combination must be avoided where there is risk of misuse or abuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking ACT BUPRENORPHINE/ NALOXONE, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see WARNINGS AND PRECAUTIONS).

Other central nervous system depressants
Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machines hazardous. Example central nervous system depressants are: other opioids (e.g. methadone, analgesics, antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine and related substances.

Opioid analgesics
The analgesic properties of other opioids may be reduced in patients receiving treatment with buprenorphine/naloxone for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving ACT BUPRENORPHINE/ NALOXONE. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining. Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see Precipitation of opioid withdrawal syndrome).

Naltrexone
Naltrexone is an opioid antagonist that can block the pharmacological effects of buprenorphine. For opioid dependent patients currently receiving ACT BUPRENORPHINE/NALOXONE treatment, the antagonist naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone treatment, the intended therapeutic effects of ACT BUPRENORPHINE/NALOXONE administration may be blocked by the naltrexone antagonist.

CYP3A4 inhibitors

Patients receiving buprenorphine should be closely monitored, and may require dose reduction if combined with potent CYP3A4 inhibitors. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC (area under the curve) of buprenorphine (50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Example CYP3A4 inhibitors include protease inhibitors, macrolide antibiotics, and azole antifungals.

CYP3A4 inducers
Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in under-treatment of opioid dependence with buprenorphine. It is recommended that patients receiving ACT BUPRENORPHINE/NALOXONE should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered, and the dose of buprenorphine or CYP3A4 inducer may need to be adjusted accordingly.

Monoamine oxidase inhibitors (MAOIs)
The concomitant use of MAOIs may produce exaggeration of the effects of opioids.

Serotonin Syndrome
Coadministration of buprenorphine/naloxone with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the

risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Alcohol

Alcohol can increase the sedative effect of opioids. Alcoholic beverages should be avoided while taking ACT BUPRENORPHINE/NALOXONE.

DOSAGE AND ADMINISTRATION

ACT BUPRENORPHINE/NALOXONE sublingual tablets should be placed under the tongue until dissolved. Cutting, breaking, crushing or chewing ACT BUPRENORPHINE/NALOXONE can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Adults:

Appropriate security measures should be taken to safeguard stocks of ACT BUPRENORPHINE/NALOXONE against diversion.

ACT BUPRENORPHINE/NALOXONE must be dispensed on a daily basis under the supervision of a healthcare professional until the patient has sufficient clinical stability and is able to safely store ACT BUPRENORPHINE/ NALOXONE take-home doses.

ACT BUPRENORPHINE/NALOXONE is indicated for substitution treatment in adults with problematic opioid drug dependence. The intention of the naloxone component is to deter injection and intranasal misuse and abuse.

Opioid drug dependence is a chronic relapsing disease; length of treatment must be tailored for each patient depending on his/her condition.

Patients prescribed ACT BUPRENORPHINE/NALOXONE should be carefully monitored within a framework of medical, social, and psychological support as part of a comprehensive opioid

dependence treatment program.

ACT BUPRENORPHINE/NALOXONE sublingual tablets should only be prescribed by physicians who meet the following requirements:

i) Experience in substitution treatment in opioid drug dependence, and
ii) Completion of a recognized Buprenorphine and Naloxone Education Program.

The Buprenorphine and Naloxone Education Program is a risk management program that is founded on the following four core components that provide for the safe and effective use of the drug within a framework of medical, social and psychological support:
- **training of the prescribing physicians in the use of Buprenorphine and Naloxone sublingual tablets;**
- **maintenance of a list of Buprenorphine and Naloxone Education Program trained physicians;**
- **daily dosing supervised by a healthcare professional, progressing to unsupervised administration as the patient's clinical stability permits;**
- **take-home doses once the patient has sufficient clinical stability and is able to safely store ACT BUPRENORPHINE/ NALOXONE. Take-home doses should be assessed and reviewed on a regular basis.**

Physicians should not prescribe ACT BUPRENORPHINE/NALOXONE sublingual tablets unless the condition of daily intake supervised by a healthcare professional can be ensured until the patient has sufficient clinical stability and is able to safely store ACT BUPRENORPHINE/NALOXONE sublingual tablets take-home doses (see WARNINGS AND PRECAUTIONS).

Physicians may obtain more information about the Buprenorphine and Naloxone Education Program by calling the following toll-free phone number: 1-866-254-6111.

Dosing Considerations

Method of Administration

ACT BUPRENORPHINE/NALOXONE sublingual tablets should be placed under the tongue until dissolved. Dissolution usually occurs within 2 to 10 minutes.

When multiple tablets are needed to achieve optimal dosage, a patient may place all tablets sublingually at the same time or in two divided portions, the second portion to be placed sublingually directly after the first portion has dissolved.

Patients should not swallow or consume food or drink until the tablet is completely dissolved.

Precautions to be taken before induction

Prior to induction with ACT BUPRENORPHINE/NALOXONE, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with ACT BUPRENORPHINE/NALOXONE should be undertaken when objective and clear signs of

withdrawal are evident.

Patients taking heroin (or other short-acting opiates):

For patients dependent on heroin or short-acting opioids, the first dose of ACT BUPRENORPHINE/NALOXONE should be started when objective signs of withdrawal appear, but not less than 6 hours after the patient last used opioids. A score equal or greater than 13 on the Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment.

Patients on methadone:

For patients receiving methadone, the methadone maintenance dose should be reduced to the minimum methadone daily dose that the patient can tolerate before beginning ACT BUPRENORPHINE/NALOXONE therapy. The first ACT BUPRENORPHINE/ NALOXONE dose should be started only when objective signs of withdrawal appear (e.g. COWS score equal or greater than 13), and generally not less than 24 hours after the patient last used methadone because of the long half-life of methadone.

Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Regular monitoring of liver function is recommended.

Recommended Dose and Dosage Adjustment

Induction:

The recommended starting dose is 8 mg ACT BUPRENORPHINE/NALOXONE on Day 1, initiating with 4 mg and then an additional 4 mg dose may be administered depending on the individual patient's requirement. The suggested total dose target for treatment on Day 1 is within the range of 8 and 12 mg.

During initiation of treatment, closer dosing supervision is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Patients with Hepatic Impairment:

ACT BUPRENORPHINE/NALOXONE is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Dose adjustments may be considered in cases of mild to moderate hepatic impairment, and patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and / or buprenorphine (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Patients with Renal Impairment:
Caution is recommended when treating patients with severe renal impairment (CL_{cr} <30 ml/min) which may require dose adjustment.

Geriatrics (>65 years of age):
Respiratory depression has occurred in the elderly when opioids were co-administered with other

agents that can depress respiration. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrating upwards slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Dose Titration :

Dosage stabilisation and maintenance therapy

Following treatment induction, the patient should be rapidly stabilised on an adequate maintenance dose by titrating to clinical effect. Dose titration in increments or decrements of 2 - 8 mg buprenorphine to a level that holds the patient in treatment and suppresses opioid withdrawal effects is guided by reassessment of the clinical and psychological status of the patient. A maintenance dose of 12 mg to 16 mg of ACT BUPRENORPHINE/NALOXONE used once daily is clinically effective for most patients. Doses should not exceed a maximum single daily dose of 24 mg.

During maintenance therapy, it may be necessary to periodically re-stabilise the patient to a new maintenance dose in response to changing patient needs.

Less than daily dosing:

Following successful induction and after the patient is receiving a stable dose, the frequency of ACT BUPRENORPHINE/NALOXONE dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient who receives a stable daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg.

In some patients, following successful induction and after the patient is receiving a stable dose, the frequency of ACT BUPRENORPHINE/NALOXONE dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.

Patients dependent upon concomitant CNS-active substances, including alcohol, should not be treated with the increased doses required by the less-than-daily dosing regimen intended for use in a supervised dose setting. Patients with sporadic use of concomitant non-opioid medications should be monitored closely, and all patients dosed on a less-than-daily basis should be observed for at least 1.5 hours following the first multi-dose administration initiating less-than-daily dosing.

Reducing dosage and terminating treatment (Medical taper):

The decision to discontinue therapy with ACT BUPRENORPHINE/NALOXONE should be made as part of a comprehensive treatment plan. To avoid withdrawal symptoms and potential relapse to illicit drug use, the ACT BUPRENORPHINE/ NALOXONE dose may be progressively decreased over time in favourable cases until treatment can be discontinued. The decision to taper should be

made by the prescriber, patient, and counsellor/support staff. The risk of relapse following withdrawal of treatment should be considered (see WARNINGS AND PRECAUTIONS).

Clinical Supervision

Treatment should be initiated with supervised administration progressing to unsupervised administration as the patient's clinical stability permits. During the initiation of treatment, closer supervision of dosing is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

As the patient becomes stabilised in treatment, longer intervals between patient assessments may be appropriate based upon patient compliance with treatment, effectiveness of the treatment plan, and overall patient progress. It is also recommended that the prescription quantity for unsupervised administration be determined with consideration for the frequency of patient visits and the patient's ability to manage supplies of take-home medication.

DRUG ABUSE AND DEPENDENCE

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed (see WARNINGS AND PRECAUTIONS).

Abuse and diversion of buprenorphine by opiate addicts has been reported (see WARNINGS AND PRECAUTIONS).

Disposal

Unused or expired ACT BUPRENORPHINE/ NALOXONE sublingual tablets should be properly disposed of to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

ACT BUPRENORPHINE/ NALOXONE should never be disposed of in household trash. Disposal via a pharmacy take- back program is recommended. Consult with a pharmacist and/or consult with www.healthsteward.ca for information on responsible pharmaceutical disposal options.

Missed Dose

Missed doses are notable as they may contribute to a loss of tolerance to buprenorphine. The more doses a patient misses, the greater the loss of tolerance. Patients should be reassessed to ensure they are receiving an appropriate dose on resumption of ACT BUPRENORPHINE/NALOXONE treatment. The resumption dose may need to be adjusted back to levels used during ACT BUPRENORPHINE/NALOXONE induction (see Recommended Dose and Dosage Adjustment, Induction).

If the patient has relapsed to full agonist opioids, the patient should be advised to suspend resumption of their ACT BUPRENORPHINE/NALOXONE until they are in moderate opioid withdrawal due to the risk of precipitated withdrawal.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and symptoms: Signs and symptoms of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed.

The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

Treatment:

In the event of overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be performed. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment where full resuscitation facilities are available.

If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Use of an opioid antagonist (e.g., naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared to its effects on full agonist opioid agents.

If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required. Initial naloxone doses may range up to 2 mg and be repeated every 2-3 minutes until a satisfactory response is achieved. Patients dosed with initial doses totalling greater than 4 mg should be monitored closely.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine has a high affinity for mu-opioid receptors, therefore reducing the binding ability, and thus the activity, of other opioids on these receptors. Buprenorphine's activity in opioid maintenance treatment is attributed to its slowly reversible link with the mu-opioid receptors in the brain, which prolongs activity at the receptor, leading to reduced opioid withdrawal symptoms.

Naloxone is an antagonist at mu-, delta-, and kappa-opioid receptors. Because of its almost complete first pass metabolism and low sublingual bioavailability, naloxone administered orally or sublingually has no detectable pharmacological activity. However, if misused or abused intranasally

or by injection, by a person dependent upon a full opioid agonist, the presence of naloxone in ACT BUPRENORPHINE/NALOXONE sublingual tablets can produce marked opioid antagonist effects that can prompt the immediate onset of opioid withdrawal symptoms as a deterrent to misuse and abuse.

Pharmacodynamics

Subjective effects

Comparison of buprenorphine with full agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opiate agonist effects, which are limited by a ceiling effect.

Buprenorphine 16 mg had opioid agonist effects similar to 4 mg intramuscular hydromorphone, and equivalent to about 30 mg intramuscular morphine.

Opioid agonist ceiling effects were also observed in a double-blind parallel group, dose ranging comparison of single doses of 1, 2, 4, 8, 16 or 32 mg buprenorphine sublingual solution (comparable approximately to 1.5 mg, 3 mg, 6 mg, 12 mg, 24 mg and 48 mg, respectively, of the tablet form), oral methadone (15, 30, 45 or 60 mg) and placebo. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid experienced, non-dependent male subjects. Both drugs produced typical opioid agonist effects. For all measures for which drugs produced an effect, buprenorphine produced a dose-related response but, in each case, there was a dose which produced no further effects. In contrast, the highest dose of methadone (60 mg) always produced the greatest effects.

Physiologic effects

Buprenorphine effects were also assessed in opioid-experienced subjects administered 12 mg sublingually or up to 16 mg by IV injection 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 blood pressure was higher for the 8 mg buprenorphine IV group than placebo. 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 solution (1, 2, 4, 8, 16 or 32 mg) were compared to those of oral methadone (15, 30, 45 or 60 mg) in non-dependent, opioid experienced healthy male volunteers. In this study, hypoventilation not requiring mechanical intervention was reported more frequently after buprenorphine sublingual solution doses of 4 mg and higher (4 mg solution comparable approximately to a 6 mg tablet dose) than after methadone at these doses tested. Both drugs decreased O_2 saturation to the same degree.

Effect of naloxone

Naloxone had no clinically significant effect when administered by the sublingual route; plasma concentrations are low and decline rapidly. Buprenorphine and naloxone, when administered sublingually even to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. In methadone-maintained patients and heroin- dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal effects that were ratio-dependent; the most intense withdrawal effects were produced by 2:1 and 4:1 ratio, less intense by an 8:1 ratio. ACT BUPRENORPHINE/ NALOXONE sublingual tablets contain buprenorphine with naloxone at a ratio of 4:1.

Central Nervous System:

Opioids produce respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Opioids depress the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Opioids cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

Gastrointestinal Tract and Other Smooth Muscle:
Opioids cause a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:
Opioids may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System:
Opioids may influence the hypothalamic-pituitary-adreno or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System:

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics

Buprenorphine

Absorption: When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. The use of this medication by the oral route is therefore ineffective.

When taken sublingually, there was a wide inter-patient variability in the absorption of buprenorphine but within subject variability was low. Plasma levels of buprenorphine increased with dose in the range of 4 mg to 16 mg, although the increase was not directly dose proportional. Mean Cmax for buprenorphine 4 mg was 2.00 ng/mL and increased to 2.65 ng/mL at 8 mg and 4.42 ng/mL at 16 mg. Mean $AUC_{0\text{-}inf}$ for sublingual tablet doses of 4 mg, 8 mg and 16 mg were, respectively, 13.90, 27.83 and 44.16 (h*ng/mL).

Distribution: Buprenorphine is highly lipophilic, which leads to rapid penetration of the blood-brain barrier. Buprenorphine is approximately 96% protein-bound, primarily to alpha and beta globulin.

Metabolism: Buprenorphine is primarily metabolized through N-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation.

Norbuprenorphine binds to opioid receptors *in vitro*; however, it is not known whether norbuprenorphine contributes to the overall effect of buprenorphine and naloxone.

Excretion: Buprenorphine is essentially eliminated in the feces by biliary excretion of the glucuroconjugated metabolites (approximately 70%), the rest being eliminated in the urine. In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). In urine, most of buprenorphine and norbuprenorphine were conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated).

The overall mean elimination half-life of buprenorphine in plasma is 37 hours, although the levels are very low 10 hours after dosing (majority of AUC of buprenorphine is captured within 10 hours), indicating that the effective half-life may be shorter.

Naloxone

Absorption: Naloxone mean peak plasma concentrations were achieved at approximately 1hr post-dose, and were measurable up to 8 hours post-dose. Across the doses of 1 mg to 4 mg, a trend towards increasing naloxone plasma exposure with an increase in dose was observed.

Naloxone has not been found to affect the pharmacokinetics of buprenorphine and both buprenorphine alone and buprenorphine/naloxone sublingual tablets deliver similar plasma

concentrations of buprenorphine.

Distribution: Following IV administration, naloxone is rapidly distributed (distribution half-life ~ 4 minutes). Following oral administration, naloxone is barely detectable in plasma; following sublingual administration of buprenorphine and naloxone, plasma naloxone concentrations are low and decline rapidly. Naloxone is approximately 32-45% protein bound, primarily to albumin.

Metabolism: The drug is metabolized in the liver, primarily by glucuronide conjugation. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as N-dealkylation, and reduction of the 6-oxo group.

Excretion: The drug is excreted in the urine. Naloxone has a mean elimination half-life from plasma of 1.3 hours.

Special Populations and Conditions

Pediatrics:
Individuals under 18 years of age should not take ACT BUPRENORPHINE/ NALOXONE tablets.

Geriatrics:
The safety and efficacy of buprenorphine and naloxone have not been established in adults over 65 years of age.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrating upwards slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment
ACT BUPRENORPHINE/ NALOXONE is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. If ACT BUPRENORPHINE/ NALOXONE is used in this patient population, caution is advised (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Both buprenorphine and naloxone are extensively metabolized by the liver. In patients with moderate and severe hepatic impairment, plasma levels and half-life values of both buprenorphine and naloxone were found to be markedly increased compared to healthy subjects. This effect was more pronounced in patients with severe hepatic impairment.

Hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, and the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. 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. Dose adjustments may be considered in

cases of mild to moderate hepatic impairment, and patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and / or buprenorphine.

As with other opioids, buprenorphine has been shown to increase intracholedochal pressure and should therefore be administered with caution to patients with dysfunction of the biliary tract.

Renal Impairment

Renal elimination plays a relatively minor role (~ 30%) in the overall clearance of buprenorphine and naloxone. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment.

STORAGE AND STABILITY

Temperature
Store at 15°C to 30°C.

SPECIAL HANDLING INSTRUCTIONS

ACT BUPRENORPHINE/NALOXONE should be kept in a safe place out of the sight and reach of children before, during and after use. ACT BUPRENORPHINE/NALOXONE should not be used in front of children, since they may copy these actions. Do not give to others.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ACT BUPRENORPHINE/NALOXONE is available as sublingual tablets:

2 mg/0.5 mg tablets: White to off-white, round tablets debossed with Actavis logo on one side and "154" on the other side, contains 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate). Bottle packages of 30 tablets.

8 mg/2 mg tablets: White to off-white, round tablets debossed with Actavis logo on one side and "155" on the other side, contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate). Bottle packages of 30 tablets.

ACT BUPRENORPHINE/NALOXONE Sublingual Tablets contain the following non-medicinal ingredients: citric acid, crospovidone, lactose monohydrate, magnesium stearate, mannitol, natural & artificial lemon flavor, povidone, pregelatinized starch, sodium citrate, and sucralose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

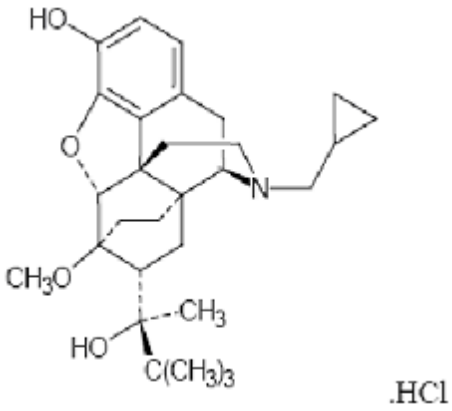
Buprenorphine

Proper name: buprenorphine hydrochloride

Chemical name: 21-Cyclopropyl-7α-[(*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-*endo*-ethano-6,7, 8,14-tetra hydrooripavine hydrochloride

Molecular formula and molecular mass: $C_{29}H_{41}NO_4$•HCl; 504.1 g/mol

Structural formula:



Physicochemical properties:

Physical Form: White or off white crystalline powder

Solubility: Sparingly soluble in water, freely soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane

pKa: Amine function: 8.5 (3.16×10^{-9})
Phenol function: 10.0 (1×10^{-10})

pH: 4.0 to 6.0

Melting Point: 272°C

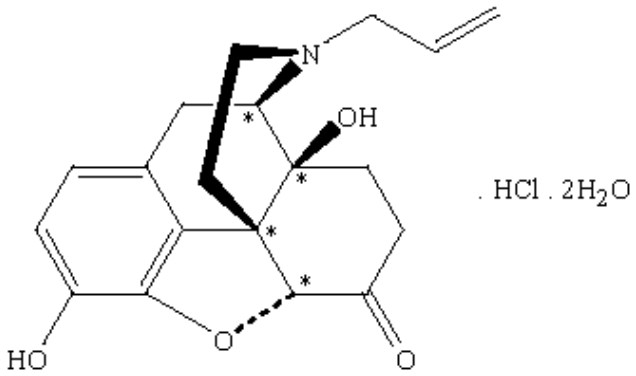
Naloxone

Proper name: naloxone hydrochloride dihydrate

Chemical name: 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride

Molecular formula and molecular mass: $C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$; 399.9 g/mol

Structural formula:



Physicochemical properties:

Physical Form: White to almost white crystalline powder.

Solubility: Soluble in water and alcohol, practically insoluble in ether, chloroform and toluene.

pKa: 7.9

pH: 2.5 to 3.5

Melting Point: 200°C - 205°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, two way crossover bioequivalence study of ACT BUPRENORPHINE/NALOXONE (Buprenorphine Hydrochloride and Naloxone Hydrochloride Dihydrate) Sublingual Tablets 8 mg/2 mg of Actavis Pharma Company and ^{N}SUBOXONE® (Buprenorphine Hydrochloride and Naloxone Hydrochloride Dihydrate) Sublingual Tablets 8 mg/2 mg of RB Pharmaceuticals Ltd., UK was performed on 45 healthy adult subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA (BUPRENORPHINE)

Buprenorphine (1 x 8 mg/2 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg.hr/mL)	25644.5 27246.1 (35.2)	25245.3 26598.3 (32.4)	101.6	94.6 - 109.0
AUC_I (pg.hr/mL)	28268.0 30009.1 (29.0)	28708.5 30188.4 (32.5)	98.5	91.1 - 106.4
C_{max} (pg/mL)	2819.6 3087.3 (44.0)	2777.9 2944.2 (36.2)	101.5	92.7 - 111.1
T_{max}§ (hr)	1.8 (0.5 - 3.0)	1.5 (0.5 - 3.5)		
$T_{½}$€ (hr)	27.5 (26.3)	29.0 (26.5)		

* ACT BUPRENORPHINE/NALOXONE (Buprenorphine Hydrochloride and Naloxone Hydrochloride Dihydrate) Sublingual Tablets, 8 mg/2 mg Actavis Pharma Company

† Suboxone® (Buprenorphine and Naloxone) Sublingual Tablets, 8 mg/2 mg, RB Pharmaceuticals Ltd., UK; purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV %) only

N=45

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA (UNCONJUGATED NALOXONE)

Free (Unconjugated) Naloxone (1 x 8 mg/2 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval#
AUC_T‡ (pg.hr/mL)	260.80 280.1 (42.0)	254.97 285.7 (51.9)	102.3	93.5 - 111.9
AUC_I (pg.hr/mL)	280.43 298.6 (42.3)	274.00 314.7 (51.2)	102.3	92.7 - 113.0
C_{max} (pg/mL)	84.16 93.0 (48.7)	78.98 87.5 (46.8)	106.6	96.8 - 117.3
T_{max}§ (hr)	0.83 (0.50 - 2.00)	0.83 (0.50 - 6.00)		
$T_{½}$€ (hr)	3.8 (70.1)	4.3 (61.9)		

* ACT BUPRENORPHINE/NALOXONE (Buprenorphine Hydrochloride and Naloxone Hydrochloride Dihydrate) Sublingual Tablets, 8 mg/2 mg, Actavis Pharma Company

† Suboxone® (Buprenorphine and Naloxone) Sublingual Tablets 8 mg/2 mg, RB Pharmaceuticals Ltd., UK, purchased in Canada.

§ Expressed as the median (range) only

€ Expressed as the arithmetic mean (CV %) only

N=43

Efficacy and safety data of the combination of buprenorphine and naloxone (Studies CR96/013 + CR96/014)

This was a one-year multicenter, placebo-controlled study comprising a 4-week randomised double-blind comparison of buprenorphine/naloxone, buprenorphine and placebo tablets followed by a 48 week open-label safety study of buprenorphine/naloxone. In the first 4-week double-blind phase, 323 heroin-addicted subjects received either placebo, buprenorphine 16 mg/day, or combination treatment of 16 mg buprenorphine + 4 mg naloxone (combination tablet) per day. For subjects randomized to active treatment dosing began with one 8 mg tablet of buprenorphine on day 1, followed by 16 mg (two 8 mg tablets) of buprenorphine on day 2. Subjects continued on 16 mg/day for four weeks. On day 3, subjects randomized to buprenorphine + naloxone were switched to the combination tablet. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Subjects received one hour of individual counselling per week and a single session of HIV education. Outcome measures were % of urine samples negative for opioids and self-reported craving for opioids.

Study Results:

The percentage of thrice-weekly urine samples that were negative for opiates was higher for subjects treated with buprenorphine (20.7%) or the combination tablet (17.8%) than for those who received placebo (both at $p<0.001$). In self-reported cravings both buprenorphine treated groups reported significantly less craving than placebo ($p<0.001$).

Comparative efficacy of buprenorphine and methadone (Study CR88/130)

This was a double-blind, double-dummy, parallel group, randomized study comparing buprenorphine ethanolic solution to methadone. One hundred sixty-two heroin dependent subjects age 21-50 years received sublingual buprenorphine (8 mg/day) or methadone (20 mg/day and 60 mg/day), during a 3-10 day induction phase, a 16-week maintenance phase and a 7 week detoxification phase. Buprenorphine was titrated to maintenance dose by day 3; methadone doses were titrated more gradually. Maintenance dosing continued through week 17, and then study drugs were tapered by approximately 70-80% per week over weeks 18-to-24, with placebo dosing for the last two weeks. Subjects received individual and/or group counselling weekly. Outcome measures were retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence.

Study Results:
Based on retention in treatment and thrice-weekly urine samples negative for opiates, the effectiveness of buprenorphine was in the same range as methadone 60 mg, but superiority was not demonstrated.

DETAILED PHARMACOLOGY

Buprenorphine

Buprenorphine is a partial mu-opioid agonist and a kappa-opioid antagonist in tests involving bremazocine-induced diuresis. Activity at the mu-opioid receptor is the basis for its use in the treatment of opioid dependence.

Binding studies in both rat and guinea-pig brain demonstrate that buprenorphine has equal, high affinity for mu- and kappa-receptor sites with approximately 10-fold lower affinity for the delta subtype and no measurable affinity for the sigma opiate receptor. *In vitro* studies show low mu, very low delta, and undetectable kappa intrinsic activity.

Unlike some partial agonists, buprenorphine produces a biphasic dose-response curve in a variety of antinociceptive tests, in its effects on blood gases, on gastrointestinal motility, EEG, catalepsy, and on respiratory rate.

Buprenorphine demonstrates a slow rate of dissociation from its receptor in *in vitro* binding studies and isolated tissue tests. This very strong association of buprenorphine for the opioid receptor is reflected by the long duration of biological action. Buprenorphine shows a corresponding insensitivity to displacement by naloxone.

Direct dependence studies in monkey and rat were negative for both withdrawal, induced by simple discontinuation of the treatment and by administration of naloxone. The low levels of physical withdrawal signs after chronic buprenorphine treatment is associated with its profile of very slow receptor kinetics and low mu intrinsic activity.

In self-administration studies in monkeys, buprenorphine was less reinforcing than other mixed agonist-antagonist analgesics, and significantly depressed the self-administration of opioids and

cocaine.

Naloxone

Naloxone is an antagonist at mu-, delta-, and kappa-opioid receptors and produces opioid withdrawal effects in opioid-dependent subjects.

Naloxone in the combination tablet (buprenorphine/naloxone) has no clinically significant effect when administered by the sublingual route because of its poor sublingual absorption and short half-life relative to buprenorphine. IV administration of buprenorphine/naloxone combinations to opioid-dependent subjects, however, produced opioid-antagonist effects and withdrawal symptoms similar in magnitude to those produced by naloxone.

TOXICOLOGY

Pre-clinical and clinical doses or exposures are compared based on the clinical dose of 16 mg/4 mg buprenorphine / naloxone, or 16 mg buprenorphine. Preclinical doses or exposures are expressed as multiples of the corresponding clinical counterpart.

Buprenorphine/naloxone

The toxicity profiles of buprenorphine and buprenorphine with naloxone in animals after a 28-day exposure period are similar in that no consistent target organ was identified, even at high oral doses.

No consistent pattern of undesirable effects was apparent in the subacute studies conducted, other than a sedative effect which is a direct consequence of the pharmacological activity of the test substance mixture.

Minimal to moderate hyperplasia of the bile duct with associated peribiliary fibrosis occurred in dogs following 52 weeks oral dosing of buprenorphine 75 mg/kg/day.

Fertility
Administration of buprenorphine/naloxone (4:1 ratio) to rats at 500 ppm or greater in the diet resulted in reduction in female fertility, whereas 100 ppm (estimated exposure approximately 5 times the human exposure from buprenorphine and naloxone 16 mg/4 mg based on plasma AUC) had no adverse effect on fertility in females.

Reproductive Toxicity
Reproduction studies with buprenorphine/naloxone indicated that embryo lethality occurred in rats in the presence of maternal toxicity at doses of 10 (oral) and 30 (intramuscular) mg/kg (buprenorphine:naloxone ratio of 1:1 at 10 mg/kg and 3:2 at 30 mg/kg). A no-effect level for this effect has not been established. No developmental toxicity was observed in rabbits at maternally toxic doses. Further, no teratogenicity has been observed in either rats or rabbits. A peri-postnatal study has not been conducted with buprenorphine/naloxone; however, maternal oral administration of buprenorphine at high doses during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight

delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

Mutagenicity
Buprenorphine/naloxone (4:1 ratio) was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*, in an *in vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in rats.

Carcinogenicity
A carcinogenicity study of buprenorphine/naloxone (4:1 ratio) in rats at dietary levels yielding doses of approximately 7, 31, and 123 mg/kg/day (4-, 18-, and 44- fold clinical exposure) showed statistically significant increases in benign testicular Leydig cell adenomas in all dose groups. No other drug-related tumours were noted.

REFERENCES

1. Amass L, *et al*. "Thrice-weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans". *Drug Alcohol Depend*; **61**: 173-181 (2001).

2. Amass L, *et al*. "Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet". *Drug Alcohol Depend* ; **58**: 143-152 (2000).

3. Bell J *et al*. "A pilot study of buprenorphine - naloxone combination tablet (Suboxone®) in treatment of opioid dependence". *Drug Alcohol Rev*; **23**: 311-317 (2004).

4. Fudala, P.J., et al., "Office-based Treatment of Opiate Addiction with a Sublingual-tablet Formulation of Buprenorphine and Naloxone." *N Engl J Med*; **349**; 10 (2003)

5. Fudala P.J., *et al*. "Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts". *Drug and Alcohol Depend*; **50**: 1-8 (1998).

6. Fudala P.J., *et al*. "Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal". *Clin Pharmacol Ther*; **47**: 525-534 (1990).

7. Hand, C.W., *et. al*., "Buprenorphine Disposition in Patients with Renal Impairment: Single and Continuous Dosing, with Special Reference to Metabolites." *Br. J Anaesthesia*, **64**: 276-282 (1990).

8. Ilett, K.F., et. al., "Estimated Dose Exposure of the Neonate to Buprenorphine and Its Metabolite Norbuprenorphine via Breastmilk During Buprenorphine Substitution Treatment" *Breastfeeding Medicine*, **7(4)**: 269-274 (2012).

9. Johnson R.E. *et al*. "A controlled comparative trial of buprenorphine and methadone treatment for opioid dependence". *JAMA*; 267: 2750-2755 (1992).

10. Johnson R.E., *et al*. "A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence". *Drug Alcohol Depend*; **40**:17-25 (1995).

11. Lidemalm, S., *et. al*., "Transfer of Buprenorphine into Breast Milk and Calculation of Infant Drug Dose." *J. Hum Lact*, **25(2)**: 199-205 (2009).

12. Ling W., *et al*. "A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence". *Arch Gen Psychiatry*; **53**: 401-407 (1996).

13. Mendelson J *et al*. "Buprenorphine and naloxone combinations: The effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers". *Psychopharmacology*;**141**: 37-46 (1999).

14. Mendelson J *et al*. "Buprenorphine and Naloxone Interactions in Opiate-dependent Volunteers". *Clin Pharmacol Ther*.; **60**: 105-114 (1996).

15. Preston K.L., *et al*. "Effects of Sublingually Given Naloxone in Opioid Dependent Human Volunteers". *Drug Alcohol Depend*.; **25**: 27-34 (1990).

16. Stoller K.B. *et al*. "Effects of buprenorphine/naloxone in opioid-dependent humans". *Psychopharmacology*; **54**: 230-242 (2001).

17. Strain E.C., Preston K.L., Liebson I.A., *et al*. "Buprenorphine Effects in Methadone- Maintained volunteers: effects at two hours after methadone". *Clin Pharmacol Ther*; **272**: 628-638 (1995).

18. Tracqui, A., *et al*., "Buprenorphine poisoning in drug abusers on substitution therapy (29 non-fatal and 20 fatal cases)". *La Presse Médicale*; **27**:12, 557-561 (1998).

19. Walsh, S.L., *et. al.*, "Acute Buprenorphine Administration in Humans: Partial Agonist and Blockade Effects." *J Pharmacol Exp Therapeutics*, **247**: 361-372 (1995).

20. Walsh S.L., *et al*. "Clinical pharmacology of buprenorphine: Ceiling effects at high doses". *Clin. Pharmacol Ther*; **55**: 569-580 (1994).

21. Product Monograph for Suboxone® (Buprenorphine and Naloxone Sublingual Tablets 2 mg/0.5 mg and 8 mg/2 mg). Manufactured by Indivior UK Limited, Berkshire, United Kingdom (Control No.: 195433; Date of Revision: December 20, 2016).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

[N]ACT BUPRENORPHINE/NALOXONE
buprenorphine (as buprenorphine hydrochloride)
and
naloxone (as naloxone hydrochloride dihydrate)

Read this carefully before you start taking ACT BUPRENORPHINE/NALOXONE and each time you get a refill. This leaflet is a summary and will not tell you everything about ACT BUPRENORPHINE/NALOXONE. Talk to your health care professional about your medical condition and treatment and ask if there is any new information about ACT BUPRENORPHINE/ NALOXONE.

Serious Warnings and Precautions

ACT BUPRENORPHINE/ NALOXONE can be misused or abused in a manner similar to other opioids, legal or illicit, which can lead to overdose and death.

When you take ACT BUPRENORPHINE/ NALOXONE it must be placed under the tongue until dissolved. Do not cut, break, crush, or chew the tablets. This can be dangerous and can lead to death or can seriously harm you.

You may get life-threatening breathing problems while taking ACT BUPRENORPHINE/ NALOXONE. This is less likely to happen if you take it as prescribed by your doctor.

You should never give anyone your ACT BUPRENORPHINE/ NALOXONE. They could die from taking it. If a person has not been prescribed ACT BUPRENORPHINE/ NALOXONE, taking even one dose can cause a fatal overdose. This is especially true for children.

If you took ACT BUPRENORPHINE/ NALOXONE while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:

- **has changes in their breathing (such as weak, difficult or fast breathing)**
- **is unusually difficult to comfort**
- **has tremors (shakiness)**
- **has increased stools, sneezing, yawning, vomiting, or fever**

Seek immediate medical help for your baby.

Babies born to mothers who have taken ACT BUPRENORPHINE/NALOXONE (for short or long periods, small or large doses) at the end of their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness), or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.

While taking ACT BUPRENORPHINE/NALOXONE, alcohol should be avoided. The combination of alcohol with ACT BUPRENORPHINE/NALOXONE may result in higher than normal levels of drug in the blood, potentially leading to an unintentional fatal overdose.

Keep ACT BUPRENORPHINE/NALOXONE in a safe place away from children.

Accidental use by a child is a medical emergency and may result in death. Never take your medicine in front of children as they will want to copy you. **If a child accidentally comes in contact with ACT BUPRENORPHINE/NALOXONE, get emergency help right away.**

Prevent theft and misuse. Never give ACT BUPRENORPHINE/NALOXONE to anyone else. Selling or giving away this medicine is against the law.

Taking ACT BUPRENORPHINE/NALOXONE with other opioids, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

What is ACT BUPRENORPHINE/ NALOXONE used for:

ACT BUPRENORPHINE/NALOXONE is part of a medical, social and psychological treatment program for adults undergoing substitution treatment for problematic opioid drug dependence.

Treatment with ACT BUPRENORPHINE/NALOXONE sublingual (under the tongue) tablets is intended for use in adults (18 years of age or older), and is voluntary.

Only a qualified doctor can prescribe ACT BUPRENORPHINE/ NALOXONE. The dose of ACT BUPRENORPHINE/ NALOXONE needs to be taken under the daily supervision of a healthcare professional until you are clinically stable and able to safely store ACT BUPRENORPHINE/NALOXONE take-home doses.

How does ACT BUPRENORPHINE/ NALOXONE work?

Buprenorphine, a component of **ACT BUPRENORPHINE/ NALOXONE,** works in the brain as other opioid drugs (e.g. morphine, methadone). If you are in withdrawal from opioid drugs, ACT BUPRENORPHINE/NALOXONE will stop the feelings of withdrawal.

ACT BUPRENORPHINE/NALOXONE also contains naloxone. When naloxone is injected, it blocks the effects of medicines and drugs like methadone, heroin, and morphine. Naloxone is added to ACT BUPRENORPHINE/NALOXONE to stop people from injecting ("shooting-up") ACT BUPRENORPHINE/NALOXONE tablets. When you use ACT BUPRENORPHINE/NALOXONE under your tongue (sublingually), as prescribed, the naloxone in ACT BUPRENORPHINE/NALOXONE should not stop the medicine's effects. However, if you inject ACT BUPRENORPHINE/NALOXONE, the naloxone can give you bad withdrawal symptoms.

Do not use ACT BUPRENORPHINE/ NALOXONE if:

- you are allergic to buprenorphine, naloxone, or to any of the ingredients in this product (see below for the complete listing of non-medicinal ingredients).

Talk to your healthcare professional about any health conditions or problems you may have, including if:

- you have severe asthma, trouble breathing, or other breathing problems.
- you have serious problems with your liver.
- you suffer from or have a history of alcoholism.
- you have heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have a planned surgery
- you are pregnant*.

*ACT BUPRENORPHINE/NALOXONE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This must be discussed with your doctor.

What are the ingredients in ACT BUPRENORPHINE/NALOXONE?

Medicinal ingredients: buprenorphine and naloxone
Non-medicinal ingredients: citric acid, crospovidone, lactose monohydrate, magnesium stearate, mannitol, natural & artificial lemon flavor, povidone, pregelatinized starch, sodium citrate and sucralose

What dosage forms does it come in?
2 mg buprenorphine/0.5 mg naloxone &

8 mg buprenorphine/2 mg naloxone tablets.

To help avoid side effects and ensure proper use, talk to your healthcare professional BEFORE you take ACT BUPRENORPHINE/NALOXONE. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse,
- have asthma, other breathing problems, or lung problems,
- have severe liver, kidney or heart disease,
- have low or decrease in blood pressure,
- have or had depression,
- suffer from chronic or severe constipation,
- have brain problem or recent head injury,
- have gallbladder problems,
- have pancreas problems,
- have adrenal gland problems, such as Addison's disease,
- have low thyroid hormone levels (hypothyroidism),
- in men: urinary disorders (especially linked to enlarged prostate),
- in women: if you are pregnant
- have problems urinating,
- have a curve in your spine that affects your breathing,
- have severe mental problems or hallucinations (seeing or hearing things that are not really there),
- suffer from migraines

Other warnings you should know about:

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to ACT BUPRENORPHINE/NALOXONE can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Drug testing for sport events:
Athletes should be aware that this medicine, due to its active substance, may cause a positive reaction to "anti-doping tests".

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Taking ACT BUPRENORPHINE/NALOXONE with benzodiazepines (medicines used to treat anxiety or sleep disorders) may cause death due to respiratory failure (inability to breathe). Some people have died from respiratory failure because they misused buprenorphine or took it while using a benzodiazepine drug, alcohol or other opioids. While you are being treated with ACT BUPRENORPHINE/NALOXONE, do not use benzodiazepines unless they have been prescribed by your doctor.

While taking ACT BUPRENORPHINE/NALOXONE, avoid drinking alcoholic beverages or taking medicines that contain alcohol. This can lead to serious side effects or a fatal overdose.

The following may interact with ACT BUPRENORPHINE/ NALOXONE:

- alcohol or other sedative drugs which may enhance the drowsiness caused by ACT BUPRENORPHINE/ NALOXONE. This includes prescription and non-prescription medications that contain alcohol. **Avoid** alcohol while you are taking ACT BUPRENORPHINE/NALOXONE. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or a fatal overdose
- opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help to reduce anxiety)

antidepressants (for depression and mood disorders). **Do not** take ACT BUPRENORPHINE/NALOXONE with MAO inhibitors (MAOi) or if you have taken MAOis in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention or treatment of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin (such as Coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- anti-retroviral drugs (used to treat certain viral infections)
- anti-fungal drugs (used to treat fungal infections)
- antibiotic drugs (used to treat bacterial infections)
- drugs used to treat high blood pressure
- some heart medication (such as beta blockers)
- grapefruit juice
- drugs used to treat migraines (e.g. triptans)

To avoid the possibility of drug interactions (one drug affecting another drug), be sure to advise your doctor or pharmacist of any other medications that you are taking.

Taking ACT BUPRENORPHINE/NALOXONE may make it difficult to get full pain relief from other opioid drugs. Make sure you tell your doctor that you are taking ACT BUPRENORPHINE/NALOXONE if they are treating you for pain.

Take exactly as directed. As with other narcotics, serious harm or death can result from misusing ACT BUPRENORPHINE/NALOXONE.

ACT BUPRENORPHINE/NALOXONE sublingual tablets must be placed under the tongue until dissolved. Do not cut, break, crush, or chew the tablets. This can be dangerous and can lead to death or seriously harm you.

You should tell your family members that you are using ACT BUPRENORPHINE/NALOXONE to treat your opioid dependence.

Usual Adult Starting Dose:
Your doctor will determine the best dose for you. During your treatment, the doctor may adjust the dose, depending upon your response. The effectiveness of this treatment depends on the dose taken, and on medical, psychological and social treatment provided.

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

After the first dose of ACT BUPRENORPHINE/NALOXONE, you may have some opioid withdrawal symptoms such as shaking, sweating, headache, pain, stomach pain, back pain, muscle aches, diarrhea, nausea, insomnia, runny nose, and watery eyes.

How to take ACT BUPRENORPHINE/NALOXONE:

Place the ACT BUPRENORPHINE/NALOXONE tablet dose under your tongue and allow it to dissolve. This usually takes within 2 to 10 minutes. **Do not** swallow the tablets. The sublingual route (under the tongue) is the **only** effective way to take this product.

How often should you take it?
Take the dose once a day.

If you need to take more than one tablet to achieve the dose your doctor has prescribed, you can either place all the tablets under your tongue at the same time, and allow them to dissolve or place them one after the other.

How long should you take it?
The length of treatment will be determined by you and your doctor.

After a time of successful treatment, the doctor may reduce the dose gradually to a lower maintenance dose. Depending on your condition, your ACT BUPRENORPHINE/NALOXONE dose may be reduced gradually until eventually stopped.

Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you. Suddenly stopping treatment may cause withdrawal symptoms.

Stopping your Medication

If you have been taking ACT BUPRENORPHINE/NALOXONE for more than a few days, you should not stop taking it all of a sudden. You should check with your doctor for directions on how to slowly stop taking it.

You should do it slowly to reduce the occurrence of withdrawal symptoms such as:

- body aches
- diarrhea
- gooseflesh
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- an unexplained fever
- weakness
- yawning

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

If you think you have taken too much ACT BUPRENORPHINE/NALOXONE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre **immediately**, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:

What do I do if I forget to take a dose?
If a single dose of this medication has been missed, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once.

In the case you have missed more than one dose of ACT BUPRENORPHINE/NALOXONE, contact your pharmacist or prescribing doctor as soon as possible.

Refilling Prescriptions for ACT BUPRENORPHINE/ NALOXONE:

A new written prescription is required from your doctor each time you need more ACT BUPRENORPHINE/NALOXONE. Therefore, it is important that you contact your doctor before your current supply runs out.

What are possible side effects from using ACT BUPRENORPHINE/NALOXONE?
These are not all the possible side effects you may feel when taking ACT BUPRENORPHINE/NALOXONE. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Side effects may include:

- Drowsiness

- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using ACT BUPRENORPHINE/NALOXONE.

Your doctor may do blood tests while you are taking ACT BUPRENORPHINE/NALOXONE to make sure your liver is okay.

Serious side effects and what to do about them			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Chest pain		✓	
Feeling depressed		✓	
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Itching	✓		
Nausea	✓		
Stomach pain	✓		
Wheezing			✓
UNCOMMON			
Convulsion or seizure			✓
Dark urine		✓	
Decreased blood pressure (dizziness, fainting, light-headedness)		✓	
Fainting		✓	
Feeling confused		✓	
Hallucination (seeing or hearing things that are not really there)		✓	
High blood sugar symptoms such as dry mouth, increased hunger, thirst, frequent urination		✓	
Jaundice (your skin or the white part of your eyes look yellow)		✓	
Light coloured stools		✓	
Loss of appetite	✓		
Low blood sugar symptoms such as feeling faint, dizzy, confused		✓	
RARE			

Serious side effects and what to do about them			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin			✓
Respiratory Depression: Slow, shallow or weak breathing.			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness.	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep unused or expired ACT BUPRENORPHINE/ NALOXONE in a secure place to prevent theft, misuse or accidental exposure.

Keep at room temperature (15°C to 30°C) in a dry place. **Keep out of sight and reach of children and pets.**

Do not use this product after the expiration date on the package. Check for signs of visible deterioration.

Disposal:

ACT BUPRENORPHINE/ NALOXONE should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about ACT BUPRENORPHINE/ NALOXONE:

- Talk to your healthcare professional
- This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Actavis Pharma Company, at: 1-866-254-6111.

This leaflet was prepared by Actavis Pharma Company.

Date Revised: March 7, 2017