NACT 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 Opioid Agonist
and
Opioid Antagonist

Guide for Prescribers

Addiction and Opioid Dependence

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial and environmental factors influencing its development and manifestations.[1] It involves behaviours that include one or more of the following (the 'four C's'):[1]

- Impaired control over drug use
- Compulsive use
- Continue to use despite harm
- Cravings

Dependence is related to tolerance and withdrawal.[1] Tolerance occurs when the person must take increasing doses to experience the same physiological effects.[1] Tolerance to the analgesic effects of opioids develops slowly, whereas tolerance to mood-altering effects begin within days.[1] Withdrawal occurs when the person using opioids chronically, abruptly discontinues or rapidly decreases his/her dose.[1] Withdrawal symptoms (Table 1) start within 6 to 12 hours after the last dose of short-acting opioids and usually peak at 2 to 3 days.[1] The physical symptoms largely resolve in 5 to 10 days.[1] Insomnia and dysphoria may last for weeks to months afterwards. [1]Opioid withdrawal does not have any medical complications, except during pregnancy.[1]

Table 1 – Withdrawal Signs and Symptoms [1]

Psychological Symptoms	Physical Symptoms	Objective Signs
• Anxiety • Craving • Insomnia	• Myalgias • Cramps • Diarrhea	• Restlessness • Lacrimation • Rhinorrhea • Yawning • Sweating • Chills • Piloerection

In opioid dependence, people are forced to escalate the amount of opioid they consume in order to experience the psychoactive effects, increased sense of energy and well-being from opioid use.[1] With continued use, patients will begin to experience intensely uncomfortable and frightening withdrawal symptoms at the end of a dosing interval.[1]

Opioid-dependent people using prescription opioids will commonly experience aberrant drug-related behaviours (Table 2). Treatment for opioid dependence will normally improve the patient's mood, relationships and work.[1]

Table 2 – Aberrant Behaviours with Problematic Use[1]

- Unsanctioned use
- Altering route of delivery
- Accessing opioids from other sources
- Accompanying conditions (e.g. addiction to other drugs)
- Repeated or severe withdrawal symptoms
- Social features (e.g. poor social function)
- Patient's view on opioid use (e.g. acknowledge addiction, strong resistance to tapering)

Buprenorphine/Naloxone

Buprenorphine is a partial mu-opioid agonist and a kappa-opioid antagonist.[2] Activity at the mu-opioid receptor is the basis for its use in the treatment of opioid dependence.[2] Buprenorphine has a lower intrinsic activity at the mu-opioid receptor compared to full mu-opioid agonists such as heroine, oxycodone or methadone.[1] Buprenorphine has a ceiling effect, where at a certain dose the opioid effects at the mu-opioid receptor plateau.[1] This ceiling dose varies based on the individual patient.[1]

Buprenorphine demonstrates a slow rate of dissociation and high affinity to the opioid mu-receptor.[1,2] These properties lead to its long half-life (24-60 hours) and low rates of sedation or euphoria at the appropriate sublingual dose.[1]

Wit the high affinity of buprenorphine to the mu-opioid receptor, it displaces other opioids from the opioid receptor.[1] This attenuates the effects of other opioids, if ingested.[1]

Naloxone is an antagonist at the mu, delta and kappa-opioid receptors and produces opioid withdrawal effects in opioid-dependent subjects.[2] 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.[2] Adding naloxone to the sublingual tablets is designed to deter people from crushing and injecting the tablet.[1] Naloxone will precipitate withdrawal symptoms when injected intravenously in a person who is dependent to opioids.[1]

Buprenorphine/Naloxone are available in 4:1 ratio combinations.[1] ACT BUPRENORPHINE/NALOXONE is available as a:[2]

- 2 mg buprenorphine/0.5 mg naloxone sublingual tablet
- 8 mg buprenorphine/2 mg naloxone sublingual tablet

ACT BUPRENORPHINE/NALOXONE Indications

ACT BUPRENORPHINE/NALOXONE (buprenorphine and naloxone) is indicated for substitution treatment in adults with problematic opioid drug dependence.[2]

ACT BUPRENORPHINE/NALOXONE Contraindications

ACT BUPRENORPHINE/NALOXONE sublingual tablet is contraindicated in

- Patients who are hypersensitive to buprenorphine, naloxone, or to any ingredient in the formulation
- 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 or 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)

Serious Warnings and Precautions

Table 3 - Serious Warnings and Precautions for ACT BUPRENORPHINE/NALOXONE[2]	
Limitations of Use	• 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 • 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
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
Interaction with other Central Nervous System Depressants	• 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 o Reserve concomitant prescribing of ACT BUPRENORPHINE/NALOXONE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate o Consider dose reduction of CNS depressants, ACT BUPRENORPHINE/NALOXONE or both in situations of concomitant prescribing o Follow patients for signs and symptoms of respiratory depression and sedation • ACT BUPRENORPHINE/NALOXONE sublingual tablets should be placed under the tongue until dissolved. Altering the tablet to take it by routes other than the indicated sublingual route can lead to serious adverse events including death. Do not cut, break, crush or chew ACT BUPRENORPHINE/NALOXONE
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
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

Warnings and Precautions

Table 4 - Warnings and Precautions for ACT BUPRENORPHINE/NALOXONE[2]	
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
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
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
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
Neurological Effects	• Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Buprenorphine should be used with caution 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. 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 • ACT BUPRENORPHINE/NALOXONE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death
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
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
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 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.).
Life-Threatening 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 by IV route and 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. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants. 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 • 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
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 initiate
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 • Withdrawal symptoms may also be associated with sub-optimal dosing
General precautions	• As with other opioids, ACT BUPRENORPHINE/NALOXONE should be used with caution in patients with the following conditions: o myxedema, hypothyroidism, or adrenal cortical insufficiency (e.g. Addison's disease); o toxic psychoses o 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
Labour 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
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 • 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 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 (CLcr <30 ml/min) which may require dose adjustment. • The effects of renal failure on naloxone pharmacokinetics are unknown
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.

Adverse Effects

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.

The most commonly observed adverse reactions in this study are consistent with opioid withdrawal or agonist effects.[2]

Please refer to the ACT BUPRENORPHINE/NALOXONE product monograph for a complete list of adverse effects.

Table 5 - Treatment-emergent adverse events reported in the pivotal clinical study of buprenorphine and naloxone (≥1.0 % of buprenorphine and naloxone -treated patients)[2]

System	Adverse effect	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	Vasodilation	29 (6.1%)
	Hypertension	17 (3.6%)
	Migraine	13 (2.8%)
Digestive	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%)
Hemic and lymphatic	Anemia	7 (1.5%)
	Ecchymosis	6 (1.3%)
	Lymphadenopathy	5 (1.1%)
Metabolism & Nutritional Disorders	Peripheral Edema	24 (5.1%)
	Weight Decreased	15 (3.2%)
	Hyperglycemia	5 (1.1%)
Musculoskeletal	Myalgia	31 (6.6%)
	Arthralgia	20 (4.2%)
	Leg Cramps	13 (2.8%)
	Joint Disorder	9 (1.9%)
	Arthritis	5 (1.1%)
Nervous	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	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%)
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	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%)

Drug Interactions

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.[2]

The drug interactions for ACT BUPRENORPHINE/NALOXONE are reviewed in Table 6.

Table 6 - Drug Interactions for ACT BUPRENORPHINE/NALOXONE[2]	
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
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
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
Naltrexone and opioid antagonists	• Patients maintained on ACT BUPRENORPHINE/NALOXONE may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations • Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of ACT BUPRENORPHINE/NALOXONE
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 Cmax 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
Serotonin syndrome	• Coadministration of buprenorphine/naloxone with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition

Considerations Prior to Initiating ACT BUPRENORPHINE/NALOXONE

Informed Consents:

It is important that patients be informed of all available treatment options to manage opioid dependence.[1] Patients should be made aware that evidence demonstrates that opioid maintenance therapy is superior to all forms of detoxification with respect to the outcomes of reducing illicit drug use, improving retention in treatment and reducing injection behaviour.[1] Other treatment options for opioid dependence that should be reviewed with the patient include:[1]

- Medical detoxification
- Psychological treatment programs
- Opioid agonist treatment

Preparation Prior to Initiating

Once the patient has provided informed consent, it is important to review the steps for preparing a patient prior to induction of buprenorphine/naloxone (Table 7).

Table 7 – Steps to Prepare for Buprenorphine/Naloxone Induction[1]
• Ensure no contraindication to buprenorphine/naloxone • If the patient has an active severe dependence to alcohol or benzodiazepines, these dependencies should be stabilized prior to initiating buprenorphine/naloxone. • A urine drug test should be conducted and interpreted and test positive for opioids. The initial urine test should screen for methadone and buprenorphine • The patient has safe travel to and from the office and are not driving or operating heavy machinery on the days of induction • A written treatment agreement between the patient and prescriber is recommended

Initiation

The authorization and training requirements for ACT BUPRRENORPHINE/NALOXONE can vary based on the province/territory of practice. All prescribers are encouraged to contact their provincial/territorial regulatory body before initiating ACT BUPRENORPHINE/NALOXONE.[1]

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.[2]

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

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.[2]

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.[2]

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 (preferably 12 hours) after the patient last used opioids. For delayed-release products, this should be increased to 12-24 hours (preferably 24 hours) before induction.[1] A score equal or greater than 13 on the Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment.[1,2]

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.[2]

Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Regular monitoring of liver function is recommended.[2]

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.[2]

Dose titration:

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.[2]

Clinical studies have shown that 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.[2] The optimal maintenance dose is one where the patient is free of opioid withdrawal symptoms for the full 24 hour dosing interval without experiencing intoxication or sedation from the medication.[1] At the maintenance dose there will also likely be an improvement in drug cravings.[1]

During maintenance therapy, it may be necessary to periodically re-stabilise the patient to a new maintenance dose in response to changing patient needs.[2]

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.[2]

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.[2]

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.[2]

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.[2]

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.[2]

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.[2]

Take-Home Dosing:

Take-home dosing of buprenorphine/naloxone can increase patient autonomy and assist patients in achieving increased flexibility with his/her daily life.[1] The guidelines define patients who take buprenorphine/naloxone into three categories (Table 8).[1]

Table 8 – Categories of Patients Newly Inducted on Buprenorphine/Naloxone[1]		
Category 1	Category 2	Category 3
• Patients who are clinically unstable to the point that they should initially not receive any take-home doses, including on weekends and holidays. For example, patients who are exhibiting: o recent injection o recent suicidality o cognitive impairment o unstable housing o ongoing opioid use o other active alcohol or drug dependencies.	• Patients whose degree of clinical stability makes initial weekend and holiday take-home doses appropriate within the first two months on the program. For example, patients who exhibit none of the features listed in the category above.	• Patients whose degree of clinical stability make it appropriate for additional take-home doses beyond weekends and holidays within the first two months on the program. For example, patients who: o have clinical stability beyond that described in category 2 o are dependent primarily on prescribed opioids from one prescriber o exhibit stable behaviour in the office and the pharmacy o have no severe psychiatric symptoms o have a particularly stable social situation o work and/or have family responsibilities that make a high number of observed doses overly restrictive and may lead to treatment drop out

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.[2]

The guidelines advice that if a patient has missed five days or less of buprenorphine/naloxone, he/she can resume the previous dose.[1] If the patient has missed 6 or more days, they will need a reduction in dose to reduce the risk of overdose.[1]

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.

More Information:

For prescribers interested in obtaining more information on buprenorphine/naloxone are encouraged to review:

- Handford C, Kahan M, Lester MD, Ordean A. Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline. Toronto: Centre for Addiction and Mental Health; 2012. It is available from the College of Physicians and Surgeons of Ontario at: https://www.cpso.on.ca/uploadedFiles/policies/guidelines/office/buprenorphine_naloxone_gdlns2011.pdf
- Please consult the ACT BUPRENORPHINE/NALOXONE product monograph for important information about adverse reactions, drug interactions, dosing/titration information. The ACT BUPRENORPHINE/NALOXONE product monograph is also available by calling Teva Canada MedInfo Services at1-800-268-4127 (option 3).

Medical Information

For healthcare professionals with specific questions about ACT BUPRENORPHINE/NALOXONE, please contact us at:

MedInfo
Medical Affairs
Teva Canada Innovation
1080 Beaver Hall Hill, Suite 1200
Montreal (Quebec) H2Z 1S8
Call toll-free at 1-800-268-4127 (option 3)
Email: DrugInfo@tevacanada.com

Pharmacovigilance Department & Reporting Instructions

You can report any suspected adverse reactions associated with the use of ACT BUPRENORPHINE/NALOXONE either to Teva Canada Limited at 1-800-268-4127 (Option 3), Telefax: 1-416-335-4472 or to the Canada Vigilance Program by one of the following 3 ways:

- Report online at http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and Fax toll-free to 1-866-678-6789, or Mail to:

Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario K1A 0K9

References

1. Handford C, Kahan M, Lester MD, Ordean A. *Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline*. Toronto: Centre for Addiction and Mental Health; 2012.

2. Actavis Pharma Company. *ACT BUPRENORPHINE/NALOXONE*. Mississauga, Ontario: Actavis Pharma Company; 2018. https://pdf.hres.ca/dpd_pm/00043970.PDF. Accessed December 8, 2018.