

# Etizolam in British Columbia's Illicit Drug Market

Etizolam is a thienodiazepine, which is chemically related to the benzodiazepine drug class. It has a benzene ring replaced with a thiophene ring - C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>S with a chemical structure of: 4-(o-Chlorophenyl)-2-ethyl-9-methyl-6H-thieno(3,2-f)-s-triazolo(4,3-a)(1,4)diazepine. Pure etizolam is a white odourless crystalline powder, practically insoluble in water.

## Is etizolam licensed in Canada?

No, etizolam is not licensed in Canada. It is a prescribed medication in India, Italy and Japan. In the US etizolam is not FDA approved but is legal for research purposes in several states. In regions where it is prescribed and in UK, where it is not prescribed but likely diverted from another country, it is usually available in tablet form.<sup>1</sup>

## What is the pharmacologic action of etizolam?

Etizolam is a full benzodiazepine GABA<sub>A</sub> receptor agonist so has similar properties to benzodiazepine drugs such as diazepam. Thus etizolam has amnesic, anxiolytic, anticonvulsant, hypnotic and sedative and muscle relaxant properties. As an anxiolytic etizolam is considered to be 5-10 times more potent than diazepam.<sup>2</sup>

**Onset and duration of action:** Oral doses have an onset of 0.5-2 hours and peak plasma concentration at 3-4 hours.<sup>3</sup> However, rapid ingested by smoking or injecting the peak serum concentrations may occur more quickly at about one hour. The parent compound has a half-life of 7-15 hours,<sup>4</sup> but its active metabolite (alpha-hydroxyetizolam) has a similarly long half-life.<sup>5</sup> Etizolam is metabolised entirely by the liver so metabolism may be reduced in liver disease.

**Acute effects of overdosing** are likely similar to benzodiazepines i.e. sedation, sleepiness, muscle relaxation, ataxia, slurred speech, and loss of consciousness. Due to the long half-life, a person with an overdose of etizolam can be sedated for many hours. Co-ingestion with alcohol or other depressants like opioids potentiate the effect and can increase toxicity.

**Dependence and withdrawal** may occur with etizolam in less than 4 weeks. Withdrawal symptoms include anxiety, headache, dizziness, tinnitus, anorexia, vomiting, nausea, tremor, weakness, irritability, palpitations, tachycardia and postural hypotension.

## Are opioids being adulterated with etizolam in BC?

We are hearing reports in BC of prolonged sedation after consuming what is thought to be opioids adulterated with etizolam.<sup>6</sup> Adulteration of fentanyl and its analogues with etizolam or benzodiazepines increases the likelihood of overdose due to the combined respiratory depressant effects. See prevalence section.

## How should I respond to an overdose with opioids and etizolam?

Naloxone should always be given when an overdose occurs as it will reverse the effects of opioids, but it is ineffective against the effects of benzodiazepines. Sedation, drowsiness, blackouts and memory loss due to etizolam may persist for hours. If a person is breathing but not conscious they should be placed in the recovery position. Administering multiple doses of naloxone when a person doesn't regain consciousness may lead to opioid withdrawal symptoms including vomiting which can be dangerous in a person who is unconscious. Resources on responding to overdoses with opioids and benzodiazepines/etizolam have been developed and are available on toward the heart website: [Do I keep giving naloxone?](#)<sup>7</sup> and [Opioids and Benzos or Etizolam.](#)<sup>8</sup>

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## Should flumazenil be used to reverse the effects of benzodiazepines/etizolam?

Flumazenil is an approved prescription drug in Canada indicated for the reversal of the central sedative effects of benzodiazepines. Benzodiazepines overdoses rarely produce life threatening respiratory depression<sup>9</sup> and most recover with supportive therapy.<sup>10</sup> In most cases the risks of using flumazenil outweigh the benefits and can cause seizures or dysrhythmias. Thus flumazenil is not recommended in the community and rarely in the hospital setting.

## What is the prevalence of etizolam in opioids in BC?

Various toxicology data show an increase in detected benzodiazepines and most is etizolam.

**BC Coroners Service** expedited toxicology between July and November 2020 found benzodiazepines were increasingly identified among illicit drug toxicity deaths.<sup>11</sup> Expedited toxicology results are available in a couple of days, but detection does not confirm the substance contributed to the death, this determination is made at the conclusion of the coroner's investigation.

**Lifelabs** report the results of urine drug screens (UDS) across BC monthly. Since April 2020, etizolam has been detected in about 60% of UDS where benzodiazepines/thienodiazepine were identified (personal communication LifeLabs).

**Alerts** between November 20 and Dec 19, 2020 all 6 community alerts identified fentanyl with benzo/etizolam.

**Drug checking** occurring at OPS sites show an increase of opioid samples testing positive for benzodiazepines.<sup>12</sup> Between January 1 and October 31st 2020, 10% of opioid samples were found adulterated with etizolam.<sup>13</sup> Etizolam in drug samples is usually at low proportions; therefore the Fourier transform infrared (FTIR) spectrometer may not detect it as the detection limit is 3-5%.<sup>14</sup>

## Can etizolam be detected by benzodiazepine (Benzo) test strips?

Benzo test strips have identified benzos in opioids (down). Etizolam has been detected by the BTNX benzo test strips although false negatives are possible.<sup>15</sup> As benzos do not readily dissolve in water, to reduce the chance of a false negative, it is recommended that the substance be placed in a 2ml tube with snap lid and shaken for 15 seconds and to wait at least 2 minutes before reading the result.<sup>16</sup> Despite using this method the sensitivity of test strips to etizolam may be 50-70%. The strips do not distinguish between the different types of benzodiazepines nor can they indicate concentration or dosage.

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