

# Buprenorphine for opioid dependence: Are there really differences between the formulations?

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## ABSTRACT

Buprenorphine and buprenorphine/naloxone sublingual tablets were approved by the FDA in 2002. In 2010, the buprenorphine/naloxone sublingual film was approved to address concerns of diversion, time for tablet dissolution, and unintentional exposure in children with the tablet. This article will compare the buprenorphine sublingual formulations in terms of pharmacokinetics, safety, diversion and misuse, cost, and patient preference. It will explore current data suggesting advantages or disadvantages of the various formulations since conclusive data are minimally available.

## KEYWORDS

Opioid, buprenorphine, buprenorphine/naloxone, dependence

## BACKGROUND

Buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) sublingual tablets are schedule III opioid medications approved by the U.S. Food and Drug Administration (FDA) in 2002 after the Drug Addiction Treatment Act of 2000 (DATA) was implemented to allow certain qualified physicians to treat opioid addiction in the office setting. In 2010 the FDA approved buprenorphine/naloxone (Suboxone®) sublingual film.<sup>1,2</sup> This article will compare the pharmacokinetics, safety, diversion and misuse, cost, and patient preference to determine the advantages and disadvantages of the buprenorphine sublingual formulations with a focus on the sublingual tablet formulations due to the lack of robust data pertaining to the buprenorphine/naloxone sublingual film. Information for this article was obtained from various manufacturers, the FDA website as well as literature search with keyword terms buprenorphine, buprenorphine/naloxone, and toxicity.

### Pharmacokinetics: Are the various formulations equivalent?

According to the Approved Drug Products with Therapeutic Equivalence Evaluations (also known as the Orange Book), both the buprenorphine and buprenorphine/naloxone sublingual tablets are AB rated in terms of therapeutic equivalence with their respective generic formulations. Although buprenorphine and buprenorphine/naloxone tablets are considered interchangeable, there are reports of patients requiring both increases and decreases in dosage when being switched.<sup>4,5</sup> In contrast, the buprenorphine/naloxone sublingual film is not AB rated compared to the

buprenorphine/naloxone sublingual tablets.<sup>3,6</sup> Pharmacokinetic variations exist not only between the sublingual film and tablet but also between the various strengths of the sublingual film.<sup>7</sup>

If a patient is being switched from the sublingual tablet to the sublingual film or vice versa, the conversion ratio is 1:1 up to 4 mg/1 mg individual doses.<sup>7,8</sup> The 2 mg/0.5 mg and 4 mg/1 mg doses of the sublingual film have similar bioavailability as the sublingual tablets. The 8 mg/2 mg and 12 mg/3 mg doses of the film have a higher reported bioavailability compared to the equivalent tablet dose. If converting a patient to the film from 8 mg/2 mg tablets or higher doses, the dose may need to be decreased. Unfortunately, there is limited and conflicting literature to guide this dose adjustment. Currently, the manufacturer does not provide a dose conversion between products.<sup>7,8</sup> Buprenorphine/naloxone sublingual film and tablets were compared in a double-blind, double-dummy randomized controlled trial evaluating various outcomes including trough levels, dissolution time, and mucoadhesion. There were no significant differences noted between the two formulations for trough levels. However, this was not a fixed-dose study and the trough outcome was based on an overall mean value for all patients' levels without regard to dosage.<sup>9</sup>

The various sublingual film dosages differ in terms of size and concentration of buprenorphine. If a patient is switched to a different combination of the film strips to achieve the same total daily dose, they need to be monitored for both over- and under-dosing since the exposure to buprenorphine may be different.<sup>7</sup>

Another pharmacokinetic difference between film and tablets is the time for dissolution. Per data on file with Reckitt Benckiser Pharmaceuticals Inc. (RBP), the mean dissolution time is 5-6.6 minutes for the film formulation compared to 7-12.4 minutes for the tablet.<sup>10</sup> In the study by Lintzeris et al., the mean dissolution time was 3 minutes compared to 4 minutes for the sublingual film versus the tablet ( $p=0.007$ ). A partial tablet may be removed from the mouth prior to complete dissolution. The major difference with the film formulation is the increased mucoadhesion limits removal despite not being completely dissolved. After 30 seconds, none of patients administered one film and 13% of patients administered two films were able to remove the whole film from their mouth. After 60 seconds, none of patients administered either one or two films were able to remove the entire film. These findings are proposed to limit the diversion and misuse of the film formulation especially when administered under observation, but the actual frequency of this type of diversion has not been established.<sup>9</sup>

### **Safety: Is there really a difference in the risk of unintentional exposures?**

Since the approval of the sublingual tablet formulations by the FDA in 2002, availability and use has greatly increased. For example, the Utah Department of Health analyzed data from 2002 through 2011 from the Utah Controlled Substance Database and Utah Poison Control Center documenting a 67-fold increase in buprenorphine prescribers (16 vs. 1,088 prescribers), a 444-fold increase in patients being prescribed buprenorphine sublingual products (22 vs. 9,793 patients), and a 13-fold increase in unintentional exposures (6 vs. 81 exposures).<sup>11</sup>

Although any unintentional exposure and harm is of concern, exposures in children are a high concern. RBP announced the discontinuation of the brand buprenorphine/naloxone sublingual tablets in September 2012 due to reports of increased rates of accidental exposure in children compared to the sublingual film.<sup>12</sup> This increase in exposures was reported by Boyer et al. with a 16-fold increase in unintentional buprenorphine exposures in children less than 6 years of age in the United States in 2008 compared to 2004 (53 vs. 907 exposures) with a total of 1,786 exposures in children occurring from 2000 to 2008.<sup>13</sup> The American Association of Poison Control Centers also reported this increase in exposures in children less than 6 years old with 1,267 exposures to one of the buprenorphine sublingual tablet formulations in 2009 compared to 196 exposures in 2006.<sup>14</sup> Overall, the number of opioid exposures increased from approximately 9 per 1,000,000 children in 2000 to 20

per 1,000,000 children in 2009. An average of 3,293 annual opioid exposures were reported in children 0 to 5 years old from 2000 through 2009.<sup>15</sup> In the literature, the outcomes of these exposures vary with reports of drowsiness with emesis resolving without any treatments; cases involving lethargy, miosis, and respiratory depression requiring hospitalization; and severe cases involving mental status changes and respiratory depression requiring opioid antagonist treatment or mechanical ventilation with the most severe outcome being death.<sup>16,17,18,19</sup> Almost all of the cases reported involve the buprenorphine sublingual tablet formulations rather than the film, which is proposed to be safer due to the unit dose child-resistant packaging. The manufacturer proposed benefits of this formulation include child-resistant unit dose packaging, improved mucoadhesion, and faster dissolution. Additionally, each individual film package has a unique 10-digit code to improve product tracking and discourage diversion.<sup>10</sup>

Most of the above reports were prior to the approval of the film, so it is too early to determine at this point if the sublingual film will hold up to this higher standard of safety. This issue will need to be continually monitored to determine if the film is actually safer or if enough time has not elapsed yet to document exposures in children. RBP has completed two child-resistance trials for the sublingual film pouch packaging. The first trial resulted in a 90% pass rate for child-resistance since 45/50 children (age 42-51 months) were not able to open at least 2 foil pouches within 10 minutes (17 total pouches opened; maximum of 8 pouches opened by one child). Of the 5 children able to open the pouches, only one child was able to do so prior to an adult demonstrating how to open the pouch and reminding the children they were allowed to use their teeth.<sup>20</sup> The second trial resulted in a 100% pass rate for child-resistance since 0/30 children (age 42-51 months) were able to open 8 foil pouches in 10 minutes with or without an adult demonstrating how to open the pouch (0 total pouches opened; children were not reminded they could use their teeth).<sup>21</sup>

### **Diversion and Misuse**

Diversion of buprenorphine sublingual products is a large concern when prescribing it for opioid dependent patients. It was reported that 61% of patients who had illicitly used buprenorphine/naloxone had obtained it from an individual with a current prescription in a cross-sectional study of patients entering opioid addiction treatment in two New England states.<sup>22</sup> The potential for diversion is not only based on the potential euphoric effects of the products, but also on factors of cost and

availability compared to other abused drugs, such as heroin availability being limited in other countries leading to higher potential for buprenorphine diversion. In addition, lack of access or funds to pay for treatment of addiction or withdrawal may spur illicit use of buprenorphine for self-treatment of opioid abuse/dependence or to decrease withdrawal symptoms.<sup>23</sup> The majority of misuse has been reported with the buprenorphine tablet through different routes, such as injection, smoking, or insufflation; however, the buprenorphine/naloxone tablet is also reported to be misused, although at a lower frequency.<sup>6,23,24,25</sup> When buprenorphine is misused, the effects range from euphoria in non-opioid dependent patients to withdrawal in opioid dependent patients, which is due to the high affinity and partial agonist activity of buprenorphine at the mu receptor.<sup>23</sup> Of those who have been reported to misuse the buprenorphine/naloxone tablet, a majority described it as a bad experience or resulting in no effects.<sup>6,24</sup> It is important to note that most of these reports were published prior to the approval of the buprenorphine/naloxone film.

Another factor to consider for diversion is the street value of these products from the perspective of both the seller and the buyer. According to StreetRx, which is a website providing anonymous user-submitted information on the street prices for prescription drugs, the buprenorphine/naloxone sublingual tablets have been bought/sold for the highest average prices so far in 2013 compared to buprenorphine/naloxone sublingual film and buprenorphine sublingual tablets, which had the lowest prices (Table 1).<sup>26</sup> These prices need to be considered only as an approximation since there is no validation of the prices submitted by the users. Due to the lowest cost and lack of naloxone, buprenorphine sublingual tablets would seem to be the more desirable product for the illicit buyer. This is only speculation and there is no evidence to support more or less diversion of each formulation based on street prices.

### Cost

The issue of cost is an important factor to consider especially when major differences in efficacy and safety are not present. Currently, buprenorphine and buprenorphine/naloxone sublingual tablets are only available generically while the buprenorphine/naloxone sublingual film is only available in brand. As noted above, RBP discontinued the brand buprenorphine/naloxone sublingual tablets due to reports of increased rates of accidental exposure in children, but Actavis, Inc. and Amneal Pharmaceuticals, LLC were approved in February

2013 to generically manufacture this sublingual tablet formulation.<sup>2,12</sup>

The recommended target dose of buprenorphine is 16 mg/day.<sup>7,8</sup> The cost of this daily dose would be approximately \$15.50/day, \$21/day, and \$17/day for the buprenorphine sublingual tablet, buprenorphine/naloxone sublingual tablet, and buprenorphine/naloxone sublingual film, respectively.<sup>27</sup> As expected, the generic buprenorphine tablets are the least expensive, which may be advantageous to utilize in the inpatient setting or clinic setting where observed administration is performed. At this time, it appears the buprenorphine/naloxone sublingual film is less expensive than the generic buprenorphine/naloxone sublingual tablets. This may change after the generic sublingual tablet formulation has been on the market for a longer period of time.

### Patient Preference

The preference of the patient for a certain formulation is also very important in order for him or her to remain compliant with treatment. Per data on file with RBP, it is reported that a majority of patients preferred the buprenorphine/naloxone film compared to the tablet with 71% of patients rating the taste of the film as neutral or better according to a discharge questionnaire collected in a 13-week, multicenter, open-label safety trial (n=159).<sup>10</sup> In the study by Lintzeris et al., 61% of patients preferred the film formulation with 35% having a strong preference for this formulation. In comparison, 23% of patients preferred the tablet formulation with only 14% having a strong preference for this formulation.<sup>9</sup>

**Table 1. Cost of Buprenorphine Sublingual Formulations**

Medication	Brand Name	Dose (mg)	Cost for 16mg/day Target Dose (\$) <sup>27</sup>	Average Street Price (\$) <sup>26</sup>
Buprenorphine SL tablets	Subutex®	2 8	15.50	17.33 (10-30) 17.58 (5-60)
Buprenorphine / Naloxone SL tablets	Suboxone®	2/0.5 8/2	21	10.33 (5-15) 15.50 (8-24)
Buprenorphine / Naloxone SL film	Suboxone®	2/0.5 8/2	17	13.40 (5-20) 15.87 (2-60)

## Conclusion

Due to limitations in the literature at this time and the lack of conclusive data available, there are no clear advantages supporting the use of one of the buprenorphine sublingual formulations in comparison to the others. The currently published data suggest advantages for the various buprenorphine sublingual formulations, including low cost for the buprenorphine tablet, less potential for misuse for the buprenorphine/naloxone tablet and film, faster dissolution time limiting diversion in observed administration settings for buprenorphine/naloxone film, and higher patient preference for the buprenorphine/naloxone film (Figure 1). In the inpatient setting, buprenorphine sublingual tablets would be preferred due to the lower cost and observed administration limiting diversion, while both buprenorphine/naloxone sublingual formulations would be preferred in the outpatient setting due to lower rates of diversion since there is no major difference in cost or efficacy at this time between these two products (Figure 1).

In the future, more comparative studies need to be completed in terms of pharmacokinetics not only comparing the resulting concentrations from equivalent doses of the various sublingual formulations, but also for equivalent doses of film strip combinations to determine if specific dosage adjustments are warranted. Continual reporting and documentation of unintentional exposures in both children and adults is important, but the specific buprenorphine sublingual formulation involved in the exposure must also be documented to determine if one formulation, such as the film, has less associated unintentional exposure risk. Finally, the implementation of standard surveys for patients entering addiction treatment could possibly help to better define the frequency of illicit buprenorphine use for each formulation, reported reasons for use, and outcomes of use. The limitation would be that data would only be collected from those seeking addiction treatment. Overall, there are no clear cut answers to completely solving the current information gaps in the literature regarding buprenorphine sublingual formulations to determine the advantages and disadvantages of each.

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## Figure 1. Buprenorphine Key Points

### Pharmacokinetics:

When switching between any of the buprenorphine sublingual formulations, the patient should be converted to the same dose.

Monitoring for both under- and over-dosing after a change in formulation is necessary due to potential differences in bioavailability.

The buprenorphine/naloxone sublingual film has a faster dissolution time and increased mucoadhesion compared to the buprenorphine/naloxone sublingual tablet.

### Safety:

Since the approval of the sublingual tablet formulations in 2002, the rate of unintentional exposures to the buprenorphine sublingual products has increased with up to a 16-fold increase reported in children less than 6 years old in the United States.

The effects of these exposures range from drowsiness with emesis resolving without treatment to mental status changes and respiratory depression requiring opioid antagonist treatment or mechanical ventilation. The most severe outcome is death.

### Diversion and Misuse:

The majority of misuse has been reported with the buprenorphine sublingual tablets although reports also exist for the buprenorphine/naloxone sublingual tablets

In terms of street price for the sublingual formulations, the buprenorphine/naloxone tablet has been sold for the highest average price and the buprenorphine tablet for the lowest average price so far in 2013.

### Cost:

Based on the recommended target dose of 16 mg/day, the buprenorphine sublingual tablet is the least expensive formulation currently available.

### Patient Preference:

A higher percentage of patients prefer the buprenorphine/naloxone sublingual film compared to the sublingual tablet.

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