

# Buprenorphine Transdermal Delivery System (BUTRANS), C-III National Drug Monograph October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

## FDA Approval Information

### Description/Mechanism of Action

- BTDS is the first 7-day sustained-action opioid formulation and the second opioid to become available as a patch in the U.S. and the only Schedule III and low-strength opioid available in a sustained-action and non-oral form for chronic pain.
- Buprenorphine is a high-affinity, slow receptor-dissociating opioid that induces analgesia primarily through partial agonist activity; i.e., intermediate intrinsic activity at the mu-opioid GTP-binding regulatory transducer protein (G-protein) coupled receptors (GPCRs). It has antagonist activity at kappa receptors, agonist activity at delta-opioid receptors, and partial agonist activity at nociceptin/orphanin FQ (NOP) receptors (also referred to as opioid receptor like-1 (ORL-1) nociceptin receptors).<sup>1,8</sup> In addition, buprenorphine may produce antinociceptive / analgesic effects through nonopioid receptor-related mechanisms not shared with other opioids.<sup>21</sup>

### Indication(s) Under Review in This Document

#### FDA-approved Use:

- Management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time.

#### Potential Off-label Uses:

- As **bridge therapy** to prevent withdrawal symptoms when converting from high-dose full mu-agonist opioid analgesics to high-dose (8–32 mg/d) sublingual buprenorphine for pain management (off-label use)<sup>1</sup>
- Use of **higher than US recommended doses**.
- Antihyperalgesic effects or neuropathic pain
- Treatment of **pruritus in primary biliary cirrhosis** (single case report)<sup>2</sup>
- **Inappropriate for acute pain and use in postoperative settings**
- **Not indicated for management of opioid use disorder / opioid addiction**

### Dosage Form(s) Under Review

5, 7.5, 10, 15, and 20 mcg/h transdermal system

### REMS

REMS    No REMS    Postmarketing Requirements  
*See Other Considerations for additional REMS information*

### Pregnancy Rating

Category C

## Executive Summary

### Efficacy

- Buprenorphine transdermal system (BTDS, 5–20 mcg/h every 7 days) seems to have a small analgesic effect size in the treatment of moderate to severe chronic noncancer pain, mainly low back pain and hip or knee osteoarthritic pain.
- The analgesic effect of BTDS is comparable to those of tramadol, oxycodone / acetaminophen and hydrocodone / acetaminophen.

### Safety

- The safety profile of BTDS has been well characterized and mainly consists of adverse reactions typical of opioids and local application site reactions associated with patches.

	<ul style="list-style-type: none"> <li>• Potential safety advantages include a lower risk of respiratory depression due to a ceiling effect on respiratory depression (in the absence of other central nervous system (CNS) depressants), milder opioid withdrawal syndrome upon discontinuation of therapy, lower potential for physical dependence, and lower potential for abuse / addiction than with Schedule II opioids.</li> <li>• The dose of BTDS does not need to be adjusted in patients with renal impairment and in elderly patients. However, caution and close monitoring are still required because of the potential for increased risk of respiratory depression.</li> <li>• QTc prolongation may occur if doses above the recommended maximum of 20 mcg/h are used.</li> </ul>
Other Considerations	<ul style="list-style-type: none"> <li>• When switching patients from oral MEDDs of 30 to 80 mg to BTDS, a patch strength of 10 mcg/h (which may be equianalgesic to an oral MEDD of 18–28 mg) is recommended as a conservative initial conversion dose.</li> <li>• The highest available BTDS strength of 20 mcg/h may be equianalgesic to an oral MEDD of 36–55 mg, whereas the product information states that the 20 mcg/h patch may not provide adequate analgesia for patients requiring greater than an oral MEDD of 80 mg.</li> <li>• In the UK, a morphine-to-BTDS equivalence ratio of 75:1 to 115:1 (average 95:1) is suggested.</li> </ul>
Projected Place in Therapy	<ul style="list-style-type: none"> <li>• BTDS may be a useful alternative to other low-strength opioid analgesic products (e.g., tramadol, codeine/acetaminophen, hydrocodone/acetaminophen, or oxycodone/acetaminophen) for patients with moderate to severe chronic low back pain or chronic osteoarthritic pain who have had an inadequate response or intolerance to nonopioid, nondrug and other low-strength opioid therapies and require around-the-clock, low-strength opioid analgesics for pain control.</li> <li>• BTDS may be more useful than other low-strength opioids in patients who have difficulty swallowing, poor or unpredictable gastrointestinal absorption (e.g., short bowel; nausea, vomiting), or renal impairment (e.g., the elderly).</li> </ul>

## Background

### Purpose for review

FDA approval (June 2010) of new formulation and indication of buprenorphine.

#### Issues to be determined:

- ✓ Evidence of need
- ✓ Does BTDS offer advantages to currently available alternatives?
- ✓ Does BTDS offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does BTDS have specific characteristics best managed by the nonformulary process, prior authorization, criteria for use?

### Other therapeutic options

There are no other partial agonist opioids marketed for pain management in the U.S. Butorphanol for injection is the only mixed agonist-antagonist opioid approved for pain on the VA National Formulary. There are no non-orally administered opioids on formulary other than fentanyl patches. Alternative oral, rectal and transdermal opioid products are shown below.

Formulary Alternatives	Other Considerations [MEDD80 *]	CFU, Restrictions or Other Guidance
Tramadol Tab, C-IV	C-IV scheduling reflects a lower likelihood of abuse, addiction and diversion than C-II and C-III [Unable to calculate MEDD80; exceeds the 400-mg recommended maximum daily dose of tramadol]	
Codeine / Acetaminophen Elixir, Tab, C-III	[MEDD80 exceeds the 240-mg recommended maximum daily dose of codeine]	
Codeine Tab, C-II	Not recommended for chronic pain management because of weak	

	analgesic effects as monotherapy [MEDD80 exceeds the 240-mg recommended maximum daily dose of codeine]	
Hydrocodone / Acetaminophen Liquid, Tab, C-II	Oral liquids vary in drug concentrations. Consider total daily dose of acetaminophen. [80 mg/d]	
Oxycodone / Acetaminophen Liquid, Tab, C-II	Consider total daily dose of acetaminophen. [53 mg/d]	
Hydromorphone, C-II, Tab	[20 mg/d]	
Morphine sulfate controlled release (MS Contin, generics) IR/SA Cap, IR/SA Tab, Liquid, Conc Soln, C-II	Those patients who require morphine-equivalent daily doses (MEDDs) of >80 mg for analgesia may not be candidates for BTDS since the maximal recommended dose of BTDS (20 mcg/h or 0.48 mg/24 h) will most likely not provide equivalent levels of analgesia.	Criteria for Use of Controlled-release Oxycodone [refers to place in therapy of morphine]
Methadone (generics) Tab, C-II	[19 mg/d]	Methadone Dosing Recommendations for Treatment of Chronic Pain  Criteria for Use of Controlled-release Oxycodone [refers to place in therapy of methadone]
Fentanyl transdermal system (DURAGESIC, generics), C-II	[22 mcg/h]	Criteria for Use, Fentanyl Transdermal Systems
Oxycodone Liquid, Tab, C-II	[53 mg/d]	
Buprenorphine and Buprenorphine / Naloxone Sublingual Tablets (generic equivalents of SUBOXONE), C-III	Available in high buprenorphine strengths ranging from 2 to 12 mg. FDA-approved for the treatment of opioid dependence under a Drug Addiction Treatment Act (DATA) 2000 waiver. Sublingual buprenorphine and buprenorphine / naloxone approved for opioid dependence / addiction have been used off-label for the treatment of patients with chronic pain <sup>1-3,4</sup> ; however, the use of high-strength sublingual buprenorphine or buprenorphine/naloxone solely for pain management is not sufficiently supported by evidence. [Unable to calculate]	Buprenorphine / Naloxone and Buprenorphine for Opioid Dependence, Criteria for Use for Office-Based Opioid Treatment (OBOT) Settings
	<b>Other Considerations</b> [MEDD80*]	<b>CFU, Restrictions or Other Guidance</b>
Hydrocodone Tab ER 24-Hour Abuse Deterrent (HYSINGLA ER), C-II	[80 mg/d]	
Hydrocodone Cap ER 12-Hour (ZOHYDRO ER), C-II		Non-abuse-deterrent formulation is on VA No Buy List
Hydromorphone Liquid and Tab ER 24-Hour Abuse Deterrent (EXALGO, generics), C-II	[20 mg/d]	
Hydromorphone Rectal Suppository 3 mg, C-II	Many factors can cause variable absorption. Not an appropriate or acceptable route for all patients. Usual dose 3 mg q6-8h (9-12	

	mg/d) [20 mg/d]
Levorphanol Tab, C-II	[11 mg/d]
Morphine Rectal Suppository 5, 10, 20, 30 mg, C-II	Many factors can cause variable absorption. Not an appropriate or acceptable route for all patients. Usual dose 10–20 mg q4h (60–120 mg/d) [80 mg/d]
Oxycodone Tab ER 12-Hour Abuse Deterrent (OXYCONTIN, generics), C-II	[53 mg/d]
Oxymorphone Tab, Solution, Tab ER 12-Hour Abuse Deterrent (OPANA, generics), C-II	[27 mg/d]
Tapentadol Tab and Tab ER 12-Hour (NUCYNTA and NUCYNTA ER), C-II	[267 mg/d]
Tramadol Cap ER 24-Hour (CONZIP), Tab ER 24-Hour (ULTRAM ER, generics), C-IV	[Unable to calculate]
*The MEDD80 shown in brackets is the total daily dose of the given opioid TO which 80 mg/d of oral morphine CONVERTS, WITHOUT ADJUSTMENT for incomplete cross tolerance, according to the Practical Pain Management Opioid Calculator [online]. Patients who require more than MEDD80 for adequate pain control will likely not be controlled with the highest dose (20 mcg/h) of BTDS. MEDD, Oral Morphine-equivalent daily dose	

### Overview of Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2015) and the Cochrane Central Register of Controlled Trials (CENTRAL) using the search terms *buprenorphine*, *transdermal*, and *BUTRANS*. The search was limited to clinical studies performed in humans. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. The Food and Drug Administration (FDA) Medical Review of BTDS studies also provided data. All randomized controlled trials and any long-term studies ( $\geq 1$  year) reported in the BUTRANS AMCP dossier<sup>5</sup> or FDA Medical Review<sup>6</sup> or published in peer-reviewed journals were evaluated in the review. Only data from published (nonconfidential) studies are summarized in this review.

- There have been 28 clinical trials involving BTDS for the treatment of osteoarthritis of the hips or knees (OAHK), chronic low back pain (CLBP) or chronic noncancer pain (mainly osteoarthritis and low back pain) in the U.S. and abroad, including the two pivotal multicenter, double-blind, randomized controlled trials in CLBP that the sponsor submitted to the FDA to support marketing approval (**Table 1**).

**Table 1 BTDS Clinical Trials by Study Design**

Study Methods	Study Design (K)	Osteoarthritis	CLBP	CNCP
<b>Double-blind Randomized Clinical Trials with Enriched Populations</b>				
Maintenance of analgesia	PCT (3)	BUP3011 <sup>TE</sup> BUP3012*		BUP3201 / Landau 2007 <sup>*7</sup>
Fixed duration (12 wks)	OXC IR ACT (2)	BUP3019 <sup>TE/F</sup>	BUP3015 / Steiner 2011 (Pivotal) <sup>*8</sup>	
	PCT (3)	BUP3014 <sup>TE</sup> BUP3025	BUP3024 / Steiner 2011 (Pivotal) <sup>*9</sup>	
<b>Double-blind Randomized Clinical Trials with Non-enriched Populations</b>				
Forced titration	OXC / APAP ACT (1)		BP96-0102	
	OXC / APAP APCT (1)	BP96-0101		
Titration to effect	HCD / APAP ACT (1)		BP98-1201 <sup>EQV</sup>	
	OXC / APAP APCT (1)		BP96-0604*	
	sIBUP CT (1)	James 2010* <sup>EQV10</sup>		
	PCT (3)	Breivik 2010 BP99-0203 / Munera 2010 <sup>*11</sup>		BUP3002
Conversion from HCD / APAP to Titrated vs. Fixed Dose of BTDS	DCT (1)	BUP3018 / Ripa 2012 <sup>12</sup>		
<b>Open-label Randomized Clinical Trials with Non-enriched Populations</b>				
Titration to effect	COD / APAP ACT (1)	Conaghan 2011 <sup>** NIF13</sup>		
	TRAM ER ACT (1)	Karlsson 2009 <sup>NIF14</sup>		
<b>Open-label, Nonrandomized Studies</b>				
Safety Extension	< 1 y (3)	BUP3012s		BUP3002s BUP3201s
	≥ 1 y (4)	BUP3011s BUP3014s BUP3019s	BUP3015s <sup>TE</sup>	
Actual use / Safety	≥ 1 y (1)			BP96-0103
Age group comparison	12 wk (1)	Karlsson 2014 <sup>NIF15</sup>		

Adapted from the BUTRANS AMCP Dossier<sup>5</sup> and used with permission from Purdue Pharma L.C.

\* Denotes p < 0.05 for a treatment difference favoring BTDS in the primary efficacy measure or treatment-emergent adverse events.

\*\* Denotes p < 0.05 for a treatment difference favoring the comparator in terms of incidence of withdrawals due to adverse events.

ACT, Active controlled trial; APAP, Acetaminophen; APCT, Active and placebo-controlled trial; COD, Codeine; DCT, Dose-controlled trial; EQV, Equivalence study; F, Failed study; HCD, Hydrocodone; NIF, Noninferiority study; OXC, Oxycodone; PCT, Placebo-controlled trial; sIBUP, Sublingual buprenorphine approved for pain management; TE, Terminated early; TRAM, Tramadol

- Six of the trials used an active comparator, two of the trials used both active and placebo comparators, nine used a placebo control, one trial used a sublingual buprenorphine formulation approved for pain management as the comparator, and one was a dose-controlled study that compared conversions to either titrated or fixed-dose BTDS regimens.
- Five studies were long-term (≥1 year in duration).
- One study evaluated the safety of BTDS in an actual use setting.
- Two studies involved elderly patients: one evaluated the safety and efficacy of BTDS in elderly patients relative to younger patients and the other evaluated the safety of BTDS in elderly residents of a supervised living environment.

## Efficacy (FDA Approved Indications)

### Review of Efficacy

The overall GRADE quality of evidence for efficacy was moderate. The majority of trials were sponsored by the drug manufacturer.

### Results of Published CLBP Trials

- *BTDS 20 Has a Small Additional Analgesic Benefit over BTDS 5 [BUP3015 / Steiner 2011, pivotal].*<sup>8</sup> In patients with moderate to severe CLBP, the treatment difference at 12 weeks was small (–0.67; 95% CI –0.99 to –0.35) and the NNT was 7 for the percentage of patients who had a response of at least 30% reduction in pain on an 11-point numerical rating scale from baseline (NRS-30) for BTDS 20 mcg/h relative to BTDS 5 mcg/h (dosed every 7 days). BTDS 20 mcg/h also showed statistically superior but very small treatment difference in sleep disturbance (–6.23 on 0–100-mm scale) and number of rescue medication doses (treatment difference, –0.5) as compared with BTDS 5 mcg/h. No significant treatment difference was seen in the Oswestry Disability Index. This was one of only two trials which provided data that allowed calculation of an NNT for ≥30% responders, and the only trial to show a statistically significant NRS-30 treatment difference. The NNT of 7 may not be comparable to NNTs calculated based on placebo-adjusted responder rates.
- *Oxycodone Immediate-release 40 Has a Small Additional Analgesic Benefit of Questionable Clinical Relevance over BTDS 5 [BUP3015 / Steiner 2011, pivotal].*<sup>8</sup> There was a statistically significant difference (–0.75 (95% CI, –1.07 to –0.44)) between oxycodone immediate-release (OxyIR) 40 mg/d and BTDS 5 mcg/h in reducing the average pain intensity. The difference in NRS-30 responder rates was not statistically significant. There were no statistically significant treatment differences for sleep disturbance, need for rescue medication and the Oswestry Disability Index.
- *BTDS 10–20 Has a Small, Clinically Relevant Analgesic Effect Relative to Placebo [BUP3024 / Steiner 2011, pivotal].*<sup>9</sup> In patients with moderate to severe CLBP who tolerated forced titration with BTDS 10 or 20 mcg/h during a run-in treatment phase, subsequent treatment for 12 weeks with BTDS (10 or 20 mcg/h) or placebo resulted in a small treatment difference in reducing average daily pain intensity on an NRS (–0.58; 95% CI –1.02 to –0.14). Treatment differences in terms of NRS-30 and post hoc NRS-50 (at least 50% reduction in pain) responder rates were not statistically significant except in a post hoc hybrid sensitivity analysis (NNT-30 of 9 and NNT-50 of 8). Statistically significant treatment differences were also seen in terms of improvements in sleep disturbance (very small treatment difference, –4.4; 95% CI –7.5 to –1.3 on 0–100 scale) and patient global impression of ‘much improved’ or ‘very much improved’ pain control (exploratory analysis; NNT of 5). There was no significant treatment difference in the number of nonopioid rescue medication doses.

### Results of Published OAHK Trials

- *BTDS Is Equivalent in Analgesic Effect to Low-strength Sublingual Buprenorphine (sIBUP) and Has a Lower Risk of Adverse Events [James 2010].*<sup>10</sup> In a 7-week, 24-center double-blind, double-dummy equivalence RCT conducted in the UK and AU, BTDS 5, 10 or 20 mcg/h every 7 days met criteria for analgesic equivalence relative to sublingual buprenorphine 0.6, 0.8 or 1.6 mg/d (approved outside the US for pain management). There were no significant treatment differences in number of rescue medication doses, sleep quality, pain interference scores, and WOMAC osteoarthritis index total scores. There was no statistically significant difference in withdrawals due to adverse events (36.4% vs. 44.2%, BTDS vs. sIBUP). BTDS treatment was associated with a lower incidence of adverse events (81% vs. 92%;  $p = 0.02$ ), with nausea, dizziness and vomiting being statistically less frequent on BTDS than sIBUP.
- *BTDS Plus Oral Acetaminophen Is Noninferior to But Less Tolerated than Oral Codeine / Acetaminophen in Patients ≥ 60 Years of Age [Conaghan 2011].*<sup>13</sup> BTDS 5–25 mcg/h every 7 days taken concomitantly with oral acetaminophen 4000 mg/d met criteria for analgesic noninferiority relative to combination codeine 64–240 mg / acetaminophen 4000 mg per day in a 22-week, 38-center open-label noninferiority RCT conducted under clinical practice conditions mainly in primary care centers in the UK. Patients were ≥ 60 years of age (mean, 71.4 years), 34% were men, and 98% were Caucasian. BTDS therapy was associated with a reduction in rescue medication by about 1 dose per day (a 33% relative reduction). There were no statistically significant treatment differences in the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index total score and sleep disturbance score. The percentages of patients who

- withdrew because of adverse events favored the codeine / acetaminophen group (77.6% vs. 46.2%;  $p < 0.05$ ), with nausea and vomiting more commonly leading to withdrawal on BTDS than codeine / acetaminophen.
- *BTDS Is Noninferior to and May Be Better Tolerated than Tramadol Extended-release Tablets [Karlsson 2009].*<sup>14</sup> BTDS 5, 10 or 20 mcg/h every 7 days met analgesic noninferiority criteria relative to tramadol extended-release (ER) tablets 150–400 mg/d. There were no significant treatment differences in rescue medication doses, sleep interference, quality of sleep, and WOMAC OA Index subscale scores. The percentage of patients reporting patient global impression of ‘good’ or ‘very good’ pain relief was 65% on BTDS and 53% on tramadol ER ( $p < 0.05$ ). The EQ-5D (health status) scores for anxiety / depression showed statistically significant improvement only in the tramadol group. Withdrawals due to adverse events occurred in 14.5% of BTDS-treated patients and 29.2% of tramadol ER patients, most commonly because of nausea. The incidence of adverse events was 88.4% on BTDS and 78.5% on tramadol ER.
  - *BTDS Has an Uncertain Analgesic Effect Size in OAHK Pain [Breivik 2010, BP99-0203 / Munera 2010].*<sup>11</sup> Trials used various atypical or outdated primary outcome measures for pain, and the results were inconsistent. BTDS showed no significant analgesic effects with BTDS using the primary efficacy measure, WOMAC OA Index for Pain; however, secondary efficacy measures for which data were not reported (daytime pain on movement and PGIC) showed statistically significant benefit. [Breivik 2010] Another trial [BP99-0203 / Munera 2010] showed that 44% of BTDS-treated patients and 32% of placebo patients were ‘treated successfully’ (where unsuccessful or failed treatment occurred if the patient discontinued early due to ‘ineffective treatment’ or endorsed ‘poor’ or ‘fair’ ratings on the Patient Satisfaction Scale). The odds ratio for treatment success was 1.66 overall ( $p < 0.05$ ). However, there was no significant treatment difference in terms of the secondary outcome, change in average pain intensity from baseline, a typical pain measure used in current trials.
  - *A Majority of Patients Can Be Converted from Hydrocodone / Acetaminophen to BTDS [BUP3018 / Ripa 2012].*<sup>12</sup> In a 29-center double-blind, double-dummy conversion RCT in the US, a majority (84%) of 203 adults with OAHK pain controlled on hydrocodone 15–30 mg / acetaminophen 1500–3000 mg total per day could be converted to titratable BTDS 10 or 20 mcg/h or fixed-dose BTDS 20 mcg/h (patches applied every 7 days) with maintenance of comparable levels of analgesia, stiffness and physical function. Conversion completion rates were similar for patients on lower (15–22.5 mg/d) and higher (>22.5–30 mg/d) doses of hydrocodone. The mean percentage of days with successful analgesia was 74% in the titratable and fixed-dose BTDS treatment groups. The titratable BTDS regimen was numerically better than the fixed-dose regimen in conversion completion rates (87% vs. 82%), withdrawals due to adverse events (10% vs. 15%) and treatment-emergent adverse events (TEAEs) (57% vs. 62%), however the rate of TEAEs increased after conversion from 11% during the hydrocodone / acetaminophen (brand VICODIN product) run-in period. Conversion to 5 mcg/h of BTDS every 7 days was not evaluated; however, the authors suggested that it may be prudent to switch some patients (e.g., those taking 15 mg or less of hydrocodone daily) to a lower patch strength before titrating up to BTDS 10 or 20 mcg/h.
  - *Analgesic Efficacy of BTDS Is Similar in Elderly and Younger Patient Groups [Karlsson 2014].*<sup>15</sup> In a 6-center open-label, noninferiority, observational study, elderly patients ( $\geq 75$  years old;  $N = 57$ ) and younger patients (50–60 years old;  $N = 65$ ) experienced comparable analgesic effects, health status, need for rescue medication, sleep disturbance, sleep quality and tolerability during 12 weeks of BTDS therapy (5–40 mcg/h every 7 days, titrated). Criteria were met for analgesic noninferiority of the elderly group relative to the younger group. The authors concluded that no age-related dosage adjustments of BTDS are needed. This study aimed to provide clinical verification of prior pharmacokinetic study results that showed similar systemic exposures to buprenorphine between the two age groups after BTDS patch application.

### Results of Published Chronic Musculoskeletal Pain Trials

- *BTDS Has an Uncertain Analgesic Effect in Chronic Noncancer Pain [BUP3201 / Landau 2007].*<sup>7</sup> The analgesic effect size of BTDS is uncertain in patients with chronic noncancer pain who were currently controlled on opioid / nonopioid combination therapy. The multicenter, double-blind, placebo-controlled, enriched RCT of BTDS used an atypical, composite outcome measure, “percentage of subjects with ineffective treatment.” “Ineffective treatment” was defined as requiring more than 1 g of acetaminophen rescue, requiring a change in dose, having difficulty keeping the patch affixed to the skin, or discontinuing treatment because of ineffectiveness without meeting any of the first three criteria. The percentage of

subjects with ineffective treatment was 51.2% in the BTDS group and 65.0% in the placebo group (OR 1.79, placebo vs. BTDS). No pain intensity measures were used.

### Systematic Reviews / Meta-analyses

The literature search found a meta-analysis<sup>16</sup> of 8 trials evaluating high-strength transdermal buprenorphine patches (TRANSTEC by Grünenthal GmbH) but found no systematic reviews or meta-analyses of BTDS matrix patches.

### Potential Off-Label Use

- As **bridge therapy** to prevent withdrawal symptoms when converting from high-dose full mu-agonist opioid analgesics to high-dose (8–32 mg/d) sublingual buprenorphine for pain management (off-label use)<sup>17</sup>
- Use of **higher than recommended US doses**. In the US, doses higher than 20 mcg/h are not recommended because of an increased risk of QTc prolongation. Buprenorphine patches for every 3- or 4-day dosing are available outside the US in higher strengths (35–70 mcg/h; TRANSTEC by Grünenthal). BTDS therapy (10–40 mcg/h every 7 days) was shown to be efficacious and relatively safe and adequately tolerated in an 8-week, manufacturer-sponsored, multicenter, double-blind, placebo-controlled crossover RCT in 78 opioid-treated patients with chronic, moderate to severe low back pain in Canada.<sup>18</sup> The analgesic effect size was small. Effectiveness continued in the 6-month open-label extension phase without evidence of analgesic tolerance. ECG analyses were available for 47 patients. None of these patients developed a QTc interval > 500 msec. Five BTDS-treated patients developed an increase of > 60 msec in QTcB interval to > 450 msec. According to the authors, there was no evidence of clinically meaningful QTc prolongation.
- For **antihyperalgesic effects or neuropathic pain**. Buprenorphine antagonism at the kappa receptor is thought to mediate an antihyperalgesic effect.<sup>19</sup> In a study involving human volunteers and experimentally induced pain, buprenorphine produced greater antihyperalgesic effects than analgesic effects.<sup>20</sup> Antihyperalgesic effects were described in a case report involving TRANSTEC<sup>21</sup> and a case report involving high-dose (≥16 mg/d) sublingual buprenorphine.<sup>22</sup> Other case reports describe improvement in neuropathic pain when usual therapies with or without opioids were switched to various formulations of buprenorphine.<sup>22,23,24</sup>
- Treatment of **pruritus in primary biliary cirrhosis** (single case report)<sup>25</sup>
- BTDS is **inappropriate for acute pain and use in postoperative** settings. Notable common adverse events leading to discontinuation in a phase 2 study included serious adverse events of apnea (2%), in which BTDS was a likely contributing factor. Others included confusion, somnolence and hostility.
- BTDS is **not indicated for the management of opioid use disorder**. There are no studies showing that the low doses delivered by BTDS will be effective (e.g., prevent withdrawal symptoms and craving) in treating patients with opioid addiction.

### Safety

(For more detailed information, refer to the product information.)

	Comments
<b>Boxed Warning</b>	<ul style="list-style-type: none"> <li>• BTDS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing, and monitor for development of these behaviors or conditions.</li> <li>• Serious, life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of BTDS to reduce the risk.</li> <li>• Accidental exposure to BTDS, especially in children, can result in fatal overdose of buprenorphine.</li> <li>• Prolonged use of BTDS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.</li> </ul>
<b>Contraindications</b>	<ul style="list-style-type: none"> <li>• Significant respiratory depression</li> <li>• Acute or severe bronchial asthma</li> </ul>

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<ul style="list-style-type: none"> <li>• Known or suspected paralytic ileus</li> <li>• Hypersensitivity to buprenorphine</li> </ul>	<hr/> <p><b>Warnings/Precautions</b></p> <ul style="list-style-type: none"> <li>• Interactions with CNS depressants: concomitant use may cause profound sedation, respiratory depression and death (consider dose reduction of one or both drugs).</li> <li>• Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: increased risk of respiratory depression (monitor closely).</li> <li>• Avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmics.</li> <li>• Hypotensive effects (monitor during dose initiation and titration).</li> <li>• Patients with head injury or increased intracranial pressure; intracranial effects of CO<sub>2</sub> retention (monitor for sedation and respiratory depression).</li> </ul> <hr/>
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**Safety Considerations**

- A total of 5,415 patients were treated with BTDS during controlled and open-label clinical development trials, with 183 patients treated for about 1 year.
- In general, the adverse event profile of BTDS consisted of typical opioid-related adverse events and application site reactions.
- The risks of adverse events were generally highest in the first 5–10 days of treatment, and on the lowest strength patch (5 mcg/h) than on the two higher-strength patches evaluated (10 and 20 mcg/h).<sup>6</sup>
- In titration-to-effect studies, the incidence of dose reductions due to adverse events was 11.8% on BTDS, 6.2% on hydrocodone / acetaminophen, 4.7% on oxycodone / acetaminophen and 1.9% on placebo.<sup>6</sup> Dose reductions due to nausea were notably more common on BTDS (5%) than on hydrocodone / acetaminophen (0.8%), oxycodone / acetaminophen (2.3%) or placebo (0%). Dose reductions due to somnolence were also higher on BTDS (3.9%) than on hydrocodone / acetaminophen (0.8%), oxycodone / acetaminophen (2.3%) or placebo (0%).
- Indirect data suggested that the risk of respiratory depression may be lower with BTDS than fentanyl transdermal system (TDS). Hypoventilation was reported in 2 (0.5%) of 377 BTDS subjects (5 episodes), 1 (1.2%) of 83 buprenorphine i.v. injection subjects and 1 (4.2%) of 24 fentanyl TDS (DURAGESIC) subjects across phase I clinical pharmacology studies.<sup>6</sup> None of the cases of hypoventilation were serious adverse events.
- Apnea occurred in postoperative patients treated with BTDS, making BTDS inappropriate for use in postoperative patients and probably patients experiencing acute cardiac or pulmonary compromise (e.g., myocardial infarction, pulmonary edema, pneumonia, or COPD exacerbation).<sup>6</sup>
- Application of external heat sources increased the maximum plasma concentration (C<sub>max</sub>) of buprenorphine by 26% to 55% relative to application without heat. Patients should be advised to avoid hot baths, sunbathing, using hot tubs, saunas, heating pads, electric blankets, heated waterbeds, or tanning lamps because of the risk of fatal overdose.
- Fever (internal heat) was not shown to alter the pharmacokinetics of buprenorphine from BTDS application. Nonetheless, as a precaution, providers should monitor patients who develop fever or increased core body temperature due to strenuous exertion for opioid side effects and adjust the BTDS dose if signs of respiratory or central nervous system depression occur.
- As with fentanyl TDS, patients, nurses and other persons applying patches to the patient’s skin will need to remember to remove the old patch before applying the new one to avoid accidental overdose.
- BTDS 40 mcg/hour (two BTDS 20 mcg/hour) was associated with prolongation of the QTc interval.
- Opioid withdrawal syndrome may occur upon switching to buprenorphine if its partial mu-agonist activity is insufficient to prevent withdrawal symptoms resulting from discontinuation of the previous opioid. Opioid withdrawal syndrome associated with switching was reported in 1 (0.8%) of 129 patients converted from an opioid / nonopioid combination to BTDS 5, 10 or 20 mcg/h, as compared with 6 (4.3%) of 138 patients converted to placebo (BUP3201 / Landau 2007).<sup>7</sup> Other cases of opioid abstinence from prestudy opioids that possibly or probably involved BTDS were identified in other clinical trials.<sup>6</sup> The incidence of opioid withdrawal syndrome associated with switching to BTDS is unclear.
- Opioid withdrawal syndrome may occur after discontinuation of BTDS, particularly if the patient is not placed on another opioid for pain management.
- Cases of BTDS abuse or suspected abuse were reported during clinical trials; however, the abuse liability or

abuse risk of BTDS was not evaluable because of methodologic limitations. The potential for abuse exists. The majority (83%) of buprenorphine remains in the patch even after 7 days of use, and buprenorphine can be extracted from the matrix-type patch for oral / transmucosal or parenteral abuse. In addition, BTDS may also be intentionally misused by other methods, such as application of multiple patches, application of external heat, application to a skin site used recently (within 21 days), and chewing patches (transmucosal absorption).

- Higher doses of naloxone and a longer time to onset of mu-receptor antagonist effects (e.g., 1–3 hours) may be required to reverse respiratory depression caused by buprenorphine overdose than are required with some of the other mu-opioid agonists.

### Adverse Reactions

Common adverse reactions	Incidence $\geq$ 5%: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash
Death / Serious adverse reactions	Most common serious adverse reactions (all $<$ 0.1%): chest pain, abdominal pain, vomiting, dehydration, and hypertension/blood pressure increased
Discontinuations due to adverse reactions	<ul style="list-style-type: none"> <li>• 24% in BTDS groups (N = 650) <ul style="list-style-type: none"> <li>○ NNTH = 9 (95% CI 6–15) relative to placebo.</li> <li>○ Rates were similar in forced-titration studies and titration-to-effect studies.</li> </ul> </li> <li>• 18% in oxycodone / acetaminophen groups (N = 150)</li> <li>• 26% in hydrocodone / acetaminophen groups (N = 130)</li> <li>• 12% in placebo groups (N = 308)</li> <li>• Most common adverse reactions leading to discontinuation (<math>\geq</math> 2%): nausea, dizziness, vomiting, headache, and somnolence</li> </ul>
Other notable adverse reactions	• Orthostatic hypotension, possible falls and syncope are known risks of opioids

### Drug-Drug Interactions

Refer to product information for details.

- *Benzodiazepines*: alter buprenorphine ceiling effect on respiratory depression (monitor; warn patients)
- *CNS Depressants (including Alcohol)*: increase risk of respiratory depression, profound sedation, coma and death (monitor; reduce dose of one or both agents)
- *CYP3A4 and 2D6 Inhibitors*: decrease buprenorphine clearance, increase plasma drug concentrations (monitor for respiratory depression and sedation; consider dose adjustments)
- *CYP3A4 Inducers*: increase buprenorphine clearance, reduce efficacy or, in patients physically dependent on buprenorphine, cause abstinence / withdrawal syndrome; discontinuation of CYP3A4 inducers may cause increase in plasma buprenorphine concentrations and result in respiratory depression (monitor for withdrawal; consider dose adjustments). Examples of CYP3A4 inducers: ritanovir, amiodarone, ketoconazole, erythromycin, grapefruit (juice).
- *Muscle Relaxants*: increase in skeletal muscle relaxant effects and respiratory depression (monitor)
- *Anticholinergics*: increased risk of urinary retention and / or severe constipation and paralytic ileus (monitor)

### Risk Evaluation

As of 28 August 2015.

Sentinel event advisories	<ul style="list-style-type: none"> <li>• <b>High alert medication:</b> The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes (opioids) which have a heightened risk of causing significant patient harm when used in error.</li> <li>• None specific for BTDS or buprenorphine. The Institute for Safe Medication Practices has issued sentinel event advisories on the fentanyl transdermal system.</li> <li>• No sentinel events (deaths, permanent harm, or severe temporary harm) have been reported for BTDS in VA ADERS.</li> </ul>
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Look-alike/sound-alike error potential	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	Buprenorphine TDS 5, 7.5, 10, 15 and 20 mcg/h	None	None	None	Buprenorphine HCl (BUPRENEX) Buprenorphine-naloxone BUPROBAN Bupropion Buspirone Butorphanol
	Butrans	None	None	None	BUPAP

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

## Other Considerations

- *Pharmacokinetic Considerations*

- The delivery rate of buprenorphine is proportional to the active surface area of each patch. The total amount of buprenorphine delivered over 7 days represents 16.8% of the total buprenorphine content and this percentage is the same for each patch strength (Table 2).<sup>6</sup>

**Table 2 Characteristics of Buprenorphine Patches**

Buprenorphine Delivery Rate (mcg/h)	Active Surface Area (cm <sup>2</sup> )	Total Buprenorphine Content (mg)	Total Amount of Buprenorphine Delivered Over 7 Days (mg)
BUTRANS 5	6.25	5	0.84
BUTRANS 7.5	9.375	7.5	1.26
BUTRANS 10	12.5	10	2.10
BUTRANS 15	18.75	15	2.52
BUTRANS 20	25	20	3.36

- Selected pharmacokinetic properties of BTDS are summarized in Table 3.

**Table 3 Selected Pharmacokinetic Properties of BTDS**

Parameter	Value
Mean absolute bioavailability (relative to i.v.)	15%
Median time to quantifiable concentration ( $\geq 25$ pg/ml)	17 h
Mean time to maximum concentration	3 days
Terminal half-life	26 h
Time to Steady-state	3 days
Metabolism	Negligible metabolism by skin ~ 97% of parent drug is hepatically metabolized CYP3A4 metabolism to norbuprenorphine (active) Glucuronidation to buprenorphine-3-glucuronide (active) and norbuprenorphine-3-glucuronide (active) <sup>26</sup>
Elimination (in a 7-day period)	IV: Biliary and renal for drug and metabolites IM: 70% biliary / fecal; 27% renal TD: Hepatic for drug; biliary / renal for metabolites

- The minimum effective plasma concentration of buprenorphine for analgesia in moderate to severe pain is 100 pg/ml.<sup>27</sup> BTDS 10 mcg/h usually achieves mean concentrations of 100 pg/ml around 24 to

48 hours after patch application and remain at 100 to 200 pg/ml for 7 days.<sup>6</sup> The systemic exposure to buprenorphine (AUC) is proportional to dose.

- The elimination half-life of transdermally absorbed buprenorphine from BTDS (26 h) is longer than intravenously-administered buprenorphine (8.6 h) because of continued absorption from a skin depot.
- *There is considerable long-term actual-use experience with buprenorphine transdermal products.* In Europe, sublingual and injectable formulations of buprenorphine have been used for pain for about 20 years, and in most European countries, a 3- or 4-day higher-strength matrix patch has been available since 2001 under the trade name of TRANSTEC (35 mcg/h, 52.5 mcg / h, or 70 mcg / h, equivalent to 0.84, 1.26 and 1.68 mg / 24 h, respectively, by Grünenthal). BTDS has been marketed in Denmark since 2003 and other European countries since 2008 as an identical 7-day low-strength matrix patch (NORSPAN by Norpharma A/S and BUTRANS [with a tall-man “T”] by Napp Pharmaceuticals in the U.K in 5 mcg/h, 10 mcg/h, or 20 mcg/h, equivalent to 0.12, 0.24 and 0.48 mg / 24 h, respectively).<sup>1</sup> In the U.K., low-strength BTDS was approved for moderate noncancer pain when an opioid is necessary for obtaining adequate analgesia, and the higher-strength TRANSTEC patch was approved for moderate to severe cancer pain and severe noncancer pain. The FDA Medical Reviews for BUTRANS included studies using the NORSPAN product.
- *Postmarketing Safety Surveillance.* Worldwide postmarketing safety data (May–Sep 2009) associated with the use of BUTRANS, NORSPAN and TRANSTEC showed that the most frequently reported adverse events included application site reactions, nausea, vomiting, pruritus, dizziness, somnolence and drug ineffective.<sup>6</sup> A postmarketing safety analysis was conducted on late-onset (ranging from days to months), sometimes severe, application site reactions associated with BUTRANS and NORSPAN in the UK (1335 cases reported through 27 Aug 2009). Many of the cases were consistent with allergic contact dermatitis.
- *There are several proposed advantages of buprenorphine over full mu-agonists.* Proposed advantages include antihyperalgesic effects (possibly via kappa-receptor antagonism),<sup>28,29</sup> a respiratory depression ceiling effect,<sup>30,31,32,33</sup> lower risk of hormonal effects,<sup>34,35,36</sup> lack of immunosuppression,<sup>37</sup> and only moderate withdrawal symptoms.<sup>38,39,40,41</sup> Lack of tolerance has also been proposed.<sup>39</sup> In addition, in contrast to transdermal fentanyl, BTDS has a lower abuse liability and is approved for initiation of opioid therapy and use in opioid-naïve patients.
- *Potentially lower risk of opioid-benzodiazepine toxicity.* Indirect data from a retrospective analysis of poison control center cases support a significantly lower rate of complications, treatment, hospitalization and major medical outcomes in association with buprenorphine (N = 72) than methadone (N = 692) when either was co-used with benzodiazepines for nonmedical purposes: respiratory depression (15.3% vs. 29.0%; p = 0.0125), coma (5.6% vs. 22.4%; p = 0.0004), hypotension (2.8% vs. 11.8%; p = 0.0161), received naloxone (15.3% vs. 60.4%), intubated (4.2% vs. 16.3%), hospitalized (43.3% vs. 67.3%), deaths (0 vs. 2.3%), major effects (life-threatening or resulted in significant residual disability or disfigurement; 1.4% vs. 18.6%; p < 0.0001 for deaths and major effects combined).<sup>42</sup>
- *Buprenorphine is also considered to have a low risk of dependence and less abuse or addiction liability.*<sup>43, 44, 45, 46</sup> Buprenorphine is considered to have a low risk of physical dependence because of the slow dissociation of buprenorphine from opiate receptors and gradual decrease in drug plasma concentrations after patch discontinuation. Buprenorphine has been deemed to have an abuse potential less than that of Schedule II prescription opioids and similar to that of other Schedule III opioids.
- *Acute or Perioperative Pain Management During BTDS Therapy.* Patients on long-term BTDS therapy who require acute or perioperative pain management (for elective or emergency surgery) should be managed by anesthesiologists and other experts familiar with managing patients who are physically dependent on opioids. These patients may require high doses and prolonged opioid therapy because of opioid tolerance and may experience opioid withdrawal symptoms if inadequately dosed on perioperative opioids. Buprenorphine has a high affinity and prolonged binding to mu-opioid receptors, and has the potential to interfere with the binding of full agonist opioids; however, pharmacologic properties, expert opinion, actual experience, and published recommendations suggest that buprenorphine does not antagonize the analgesic effects of other opioids.<sup>47</sup> There are limited clinical studies showing a lack of antagonistic effects when other perioperative opioids are used concomitantly with transdermal buprenorphine.<sup>48,49</sup> Another consideration is that transdermal absorption of opioids may be increased by up to 50% because of general or regional anesthesia-induced vasodilation.<sup>47</sup> There is no contraindication to continuing use of stable, long-term doses of transdermal opioids during the perioperative period; supplemental short-acting full mu-agonist opioids should be added to titrate to the desired level of analgesia.<sup>47</sup> Alternatively, BTDS may be switched to an appropriate dose of oral opioid, preferably at

least 3 days before surgery.<sup>50</sup> Switching to a full agonist opioid may be a consideration if elective surgery is planned or if the clinician prefers to avoid the potential for increased absorption of buprenorphine due to vasodilation.<sup>50</sup> Since perioperative analgesic requirements may be unpredictable, patient pain intensity, level of sedation and respiratory rate should be closely monitored.

- REMS. BTDS is covered under the Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (ER/LA Opioid Analgesics REMS).

## Dosing and Administration

- Refer to the product information for full dosing information.
- Doses of 7.5, 10, 15, and 20 mcg/hour are for opioid-experienced patients only.
- BTDS should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

### Initial Dosing

- Use of BTDS as the First Opioid Analgesic
  - BTDS treatment should be initiated with a 5 mcg/hour patch.
  - Patients should be monitored closely for respiratory depression, especially within the first 24-72 hours of initiating therapy.
- Conversion from Other Opioids to BTDS
  - *General Considerations*
    - All other around-the-clock opioid drugs should be discontinued when BTDS therapy is initiated.
    - There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids.
    - Actual *conversion* doses are not necessarily *equianalgesic* doses, and equianalgesic dose ratios may differ by the order of switching opioids and the reasons for switching (e.g., for adverse reactions or inadequate analgesia).
    - The *conversion* doses recommended in the US product information are conservative; therefore, supplemental short-acting opioid therapy will likely be necessary to achieve adequate analgesia when converting from another opioid to BTDS, and opioid abstinence symptoms may occur if the substitute and supplemental opioid doses are insufficient to prevent opioid withdrawal in patients who are physically opioid-dependent.
  - *Prior Total Daily Dose of Opioid Less than 30 mg of Oral Morphine Equivalents per Day:*
    - BTDS 5 mcg/hour should be initiated at the next dosing interval.
  - *Prior Total Daily Dose of Opioid Between 30 mg to 80 mg of Oral Morphine Equivalents per Day:*
    - The patient's current around-the-clock opioids should be tapered for up to 7 days to no more than an oral morphine-equivalent daily dose (MEDD) of 30 mg before beginning treatment with BTDS.
    - Then BTDS 10 mcg/hour should be initiated at the next dosing interval.
    - Patients may use short-acting analgesics as needed until analgesic efficacy with BTDS is attained.
  - *Prior Total Daily Dose of Opioid Greater than 80 mg of Oral Morphine Equivalents per Day:*
    - BTDS 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents.
    - An alternate analgesic should be considered.
  - *Conversion from Methadone to BTDS*
    - Close monitoring is of particular importance.
    - The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure.
- Conversion from BTDS to Other Opioids
  - The US product information does not address conversions from BTDS to other opioids, and gives no specific advice on *conversion* doses when switching BTDS to other opioids or on any *equianalgesic* doses.
  - Napp Pharmaceutical's UK BUTRANS Information for Healthcare Professionals advises the following steps when converting from BTDS to oral opioids<sup>50</sup>:

- As a general rule, wait at least 24 hours after removal of the BTDS before starting the subsequent opioid.
  - If the patient is in pain, provide immediate-release analgesics as needed (p.r.n.) for the first 3 days after removal of the patch.
  - After the 3-day period, assess the patient’s analgesic requirements based on the p.r.n. medication, then convert to the subsequent oral opioid analgesic.
- **Equianalgesic Dose Variance**
  - On a mg-per-mg basis, buprenorphine was originally thought to be 25 to 50 times more potent than morphine as an analgesic.<sup>51</sup> Pivotal trials did not seek to determine clinically equianalgesic doses of buprenorphine. More recent data suggest that buprenorphine may be 75 to 100 times more potent than morphine.<sup>52</sup> A BTDS-to-morphine equianalgesic ratio of 1:75 has been proposed,<sup>53</sup> but according to the FDA medical review, not confirmed clinically.<sup>6</sup> An MEDD-to-transdermal buprenorphine ratio of 110:1 to 115:1 has been suggested; however, caution should be used since the ratio was based on the findings of a retrospective prescription database study.<sup>54</sup>
  - The UK BUTRANS Information for Healthcare Professionals used an MEDD-to-BTDS ratio of 95:1 (midpoint of the range, 75:1 to 115:1) and provides the equianalgesic doses shown in Table 4.

**Table 4 Analgesic Dose Equivalences**

Product	Dose	Oral MEDD (mg/d)	
BuTrans 7-day patch	5 mcg/h	9–14	Source: BUTRANS Information for Healthcare Professionals (UK) <sup>50</sup> MEDD, Morphine-equivalent daily dose
	10 mcg/h	18–28	
	20 mcg/h	36–55	
Codeine / Dihydrocodeine, oral	60 mg/d	6–18	
	120 mg/d	12–36	
	240 mg/d	24–73	
Tramadol, oral	100 mg/d	10–17	
	200 mg/d	20–33	
	300 mg/d	30–50	
	400 mg/d	40–67	

- There is limited information on equianalgesic dose ratios (Table 5). The findings of published studies suggest that the estimated equianalgesic ratio of morphine oral to any buprenorphine transdermal product is 70:1 to 75:1; however, with differences in methods across studies, including different product pharmacokinetics, the direction of switching opioids and calculation of MEDDs, the range varied from 45:1 to 107:1.

**Table 5 Preliminary Equianalgesic Doses: Prospective Conversion Studies in Patients with Stable Pain**

Opioid Dose (mg/d)	Buprenorphine TD Dose	Opioid:tdB Ratio (mg) <sup>§</sup>	MEDD:tdB Ratio (mg) <sup>§</sup>	K (N)	Reference
<i>Other Opioid Converted to BTDS</i>					
Morphine, oral	—	75:1	75:1	3 (65)	Mercadante (2011) <sup>55</sup>
<i>Other Opioid Converted to TRANSTEC or Unspecified Transdermal Buprenorphine</i>					
Fentanyl TDS 25–50 mcg/h (0.6–1.2 mg/d)	35–70 mcg/h (0.8–1.6 mg/d)	0.6–0.8:1	45–60:1	1 (22)	Mercadante, Porzio (2007) <sup>56</sup>
Morphine 120–240, oral	—	70:1	70:1	1 (10)	Mercadante, Casuccio (2009) <sup>57</sup>
Fentanyl TDS 50–100 mcg/h (1.2–2.4 mg/d)	—	0.8:1	60:1		
<i>TRANSTEC or Unspecified Transdermal Buprenorphine Converted to Another Opioid</i>					
Tapentadol ER 100, 200 or 300 ± p.r.n. IR, oral	21.5 mcg/h (0.52 mg/d), mean	263–281:1	107:1 <sup>†</sup>	1 (48)	Steigerwald (2013) <sup>58</sup>

tdB, Transdermal buprenorphine (BUTRANS, TRANSTEC or unspecified transdermal buprenorphine product); <sup>†</sup> Ratio reported by study authors; <sup>§</sup> tdB 1 mg per day is equivalent to 42 mcg/h

### Titration and Maintenance of Therapy

- The minimum titration interval is 72 hours, based on the pharmacokinetic profile and time to reach steady state levels.
- **A dose of one 20 mcg/hour BTDS should not be exceeded** because of the risk of QTc interval prolongation.
- For the use of two patches, patients should be instructed to remove their current patch, and apply the two new patches at the same time, adjacent to one another at a different application site.

### Discontinuation of BTDS Therapy

- The dose should be gradually titrated downward every 7 days to prevent signs and symptoms of withdrawal in the physically dependent patient; the use of an appropriate immediate-release opioid medication should be considered.
- BTDS should not be abruptly discontinued.

### Dosage Adjustments in Special Populations

- The product information gives no recommendations for dosage adjustments in patients with renal impairment, patients with hepatic impairment and the elderly.
- In severe (Child-Pugh C) hepatic impairment, providers should consider using an alternate agent with greater dosing flexibility.

### Administration Instructions

- Patients should apply BTDS to the upper outer arm, upper chest, upper back or the side of the chest on either side of the body (total of 8 application sites).
- Patients should be instructed to wait a minimum of 21 days before reapplying BTDS to the same skin site. Reapplication of BTDS to the same site before 21 days may result in increased drug absorption.
- If problems with adhesion of BTDS occur, the edges may be taped with first aid tape. If problems with lack of adhesion continue, the patch may be covered with waterproof or semipermeable adhesive dressings suitable for 7 days of wear.
- If BTDS falls off during the 7-day dosing interval, the patient should dispose of the transdermal system properly and place a new BTDS patch on at a different skin site.
- If the buprenorphine-containing adhesive matrix accidentally contacts the skin, the area should be washed with water. Patients should be advised to avoid using soap, alcohol, lotions, oils or other products to wash skin where the adhesive matrix accidentally contacted skin or to remove any leftover adhesive from a patch because this may increase drug absorption.

### Disposal

- Patients may dispose of used or unused BTDS in the trash by sealing the patches in the Patch-Disposal Unit packaged with BTDS.
- Alternatively, patients can dispose of used patches by folding the adhesive side of the patch to itself, then flushing the patch down the toilet immediately.

## Special Populations (Adults)

### Elderly

- Of 5,415 subjects in the clinical trials, 1,377 patients aged 65 years and older received BTDS. Of those, 457 patients were 75 years of age and older.
- In the clinical program, the incidences of selected BTDS-related adverse events were higher in older subjects.
- The incidences of application site adverse events were slightly higher among subjects < 65 years of age than those  $\geq$  65 years of age for both BTDS and placebo treatment groups.
- Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in elderly patients to ensure safe use.
- A Swedish Prescribed Drug Register (SPDR) study investigated the dose pattern of BTDS (NORSPAN) to interpret whether there was possible development of tolerance and/or dependence / addiction.<sup>59</sup> Of the 7,099 patients enrolled, 1,114 (15.7%) were 60–74 years of age and 4,917 (69.3%) were 75 years of age or older. The average dose over the entire course of treatment (average, 260 days) increased by 4 mcg/h, suggesting that tolerance and dependence / addiction were not major safety issues in a mainly elderly population.
- Other studies showing that transdermal buprenorphine is effective and safe have used a high-strength matrix transdermal patch available in Europe, called TRANSTEC. An observational study showed the analgesic effectiveness and safety of TRANSTEC (median, 35 mcg/h every 4 days) in 93 older elderly patients (mean age, 79.7 years) with chronic noncancer pain, mainly due to

	osteoarthritis. <sup>60</sup> ECGs were not evaluated.
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>• Pregnancy Category C</li> <li>• Prolonged use of opioids during pregnancy may result in physical dependence in the neonate and result in neonatal opioid withdrawal syndrome shortly after birth.</li> <li>• Opioids cross the placenta and may cause respiratory depression in neonates.</li> <li>• Opioids can prolong labor, although this effect is not consistent and can be offset by an increased rate of cervical dilatation, which tends to shorten labor.</li> </ul>
<b>Lactation</b>	<ul style="list-style-type: none"> <li>• Buprenorphine is excreted in breast milk.</li> <li>• Opioid withdrawal symptoms can occur in infants when mothers discontinue BTDS therapy.</li> <li>• Discontinue nursing or discontinue the drug, taking into account the importance of the medication to the mother.</li> </ul>
<b>Renal Impairment</b>	<ul style="list-style-type: none"> <li>• BTDS has not been studied in patients with renal impairment.</li> <li>• Estimated creatinine clearance rates and steady-state buprenorphine plasma concentrations showed no apparent relationship during BTDS therapy.</li> <li>• Buprenorphine plasma concentrations after i.v. administration have been shown to be similar in patients with normal renal function and those with impaired renal function or renal failure.</li> <li>• In a study evaluating a transdermal buprenorphine product marketed outside the US (up to 70 mcg/h) in patients with chronic pain who received intermittent hemodialysis for end-stage renal disease, no significant differences were observed between pre- and post-hemodialysis buprenorphine plasma concentrations.</li> </ul>
<b>Hepatic Impairment</b>	<ul style="list-style-type: none"> <li>• Buprenorphine and norbuprenorphine exposure did not increase in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment.</li> <li>• Changes in drug exposure were not evaluated in patients with severe hepatic impairment.</li> <li>• Consider an alternate analgesic that may permit more dosing flexibility in patients with severe (Child-Pugh C) hepatic impairment.</li> </ul>
<b>Pharmacogenetics/genomics</b>	<ul style="list-style-type: none"> <li>• P-glycoprotein (P-gp) gene polymorphism may affect risk of respiratory depression of buprenorphine. Decreased expression or function of P-gp has been suggested as a factor that may explain increased risk of toxicity, particularly in children.<sup>61,62</sup> P-gp may protect against toxicity of buprenorphine by facilitating the efflux of norbuprenorphine across the blood brain barrier. However, animal studies show that P-gp expression affects antinociceptive but not respiratory effects of norbuprenorphine.<sup>63</sup></li> </ul>

### Projected Place in Therapy

- Chronic noncancer pain is very common in VA and it is important to make different opioid options available because the biopsychosocial manifestations, patient perceptions and patient responses to treatments vary widely.
- Musculoskeletal diseases have been shown to be the most frequent diagnoses (46.6%) in cumulative data of hospitalization and outpatient visits made by 324,846 Operation Enduring Freedom (Afghanistan) and Operation Iraqi Freedom (OEF-OIF) Veterans from October 2001 to June 2007.<sup>64</sup> In one study (September 2001–September 2009) of OEF-OIF Veterans, the prevalence of back problems, joint disorders and musculoskeletal / connective tissue disorders increased over time after the end of deployment, and are more common in women than men. By 7 years after returning from deployment, the prevalences in female and male Veterans, respectively, were 19.6% and 17.2% for back pain diagnoses; 19.5% and 16.7% for joint disorders; and 12.4% and 9.6% for musculoskeletal conditions.<sup>65</sup>
- BTDS is the first 7-day sustained-action opioid formulation and the second opioid to become available as a patch in the U.S. and the only Schedule III opioid available in a sustained-action form for chronic pain.
- Having moderate intrinsic mu-receptor activity and a subcellular mechanistic profile different from those of full mu-agonist opioid analgesics, buprenorphine in a patch formulation may be a useful alternative to other low-strength opioid analgesic products (e.g., tramadol, codeine/acetaminophen, hydrocodone/acetaminophen, or

oxycodone/acetaminophen) for patients with moderate to severe chronic low back pain or chronic osteoarthritic pain who have had an inadequate response or intolerance to nonopioid and non-drug therapies and require around-the-clock, low-strength opioid analgesics for pain control. BTDS may be more useful than other low-strength opioids in patients who have difficulty swallowing, poor or unpredictable gastrointestinal absorption (e.g., short bowel; nausea, vomiting), or renal impairment (e.g., the elderly).

- BTDS therapy involves trade-offs between the relatively small analgesic benefits (NNTs of 5 to 9) and risk of adverse reactions that lead to treatment discontinuation (NNTH of 9), and the trade-offs are somewhat uncertain in pain conditions other than chronic low back pain, based on available clinical study results.
- An international expert panel published a consensus statement report supported by Grünenthal GmbH (manufacturer of the high-strength buprenorphine patch, TRANSTEC).<sup>66</sup> The panel recommended buprenorphine as the top opioid of choice for the management of elderly patients with severe chronic pain because dosage adjustments are not needed in the presence of renal impairment. In addition, buprenorphine is the only opioid that has a ceiling for respiratory depression in the absence of other CNS depressants. The panel recommended buprenorphine but could not recommend morphine and fentanyl when providers want to limit the risk of immunosuppressive effects of opioids, such as in elderly patients.
- Although net benefits may be better with BTDS than certain other opioids in patients with kidney impairment or fluctuating kidney function and in elderly patients, caution and close monitoring are still required because of the potential for increased risk of respiratory depression.
- In certain individuals, BTDS may be preferred over Schedule II opioids because of a lower abuse or addiction liability; however, the incidence of BTDS abuse or addiction during actual clinical use has not been evaluated, and the potential for BTDS abuse and addiction still call for the same risk management strategies required of other opioids.
- A limited number of reports suggest that BTDS may have potential benefits in individuals with opioid-induced hyperalgesia or neuropathic pain.

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## Appendix A: GRADEing the Evidence

### Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.