Summary

The sublingual (SL) and buccal (BUC) routes of medication administration for transmucosal absorption is well-recognized and is considered safe and effective for a variety of prescription (Rx) medications (eg, fentanyl, buprenorphine, nitroglycerin, zolpidem). Some over-the-counter (OTC) medications (eg, diphenhydramine, loratadine) and natural supplements (eg, melatonin, cyanocobalamin) are pharmaceutically designed as sublingual tablets, drops, or films and produce a combination of transmucosal absorption as well as oral delivery through passive swallowing of saliva with dissolved drug from the dosage form. Both Rx and OTC dosage SL/BUC dosage forms are beneficial for children unable to swallow intact tablets and capsules when a solid dosage form is preferred over liquids. Adults with dysphagia or cognitive impairment that limits ability to swallow intact capsules or tablets also benefit from SL/BUC dosage forms. SL/BUC administration may provide a more rapid onset of therapeutic effect when compared to traditional oral tablets or capsules.

Value of petition: petition for SL or BUC administration of medical cannabis products would provide an additional ROA for adults with dysphagia or cognitive impairment as well as for children who haven't yet developed the ability or desire to swallow intact tablets or capsules and for whom chewable edible medical cannabis products is difficult due to dentition concerns or presents a choking hazard. Because of the likelihood that some patients are already using oral tinctures and oils via SL or BUC route despite package labeling specific for oral ingestion, adding SL or BUC administration approval would allow additional patient/caregiver educational materials regarding this ROA.

Concerns with petition: petition suggests SL/BUC are equivalent as ROA and conflates SL/BUC administration with SL/BUC absorption; neither of these is pharmacologically correct. Design and manufacture of SL or BUC medical cannabis products may vary by cultivator/processor/dispensary licensee meaning that patients may not receive expected benefit from SL or BUC product from different dispensaries. Petition relies heavily on pre-existing data from a specific transmucosal commercially available product [not available in US, nabiximols (Sativex®)] but provides little consideration to potential altered absorption of SL or BUC products based on formulations and patient-specific factors. Petition lists no unknown adverse effects with SL or BUC ROA, however prescribing information included in package labeling for nabiximols provides a list of adverse reactions including tooth discoloration, oral mucosal disorder, oral mucosal discoloration, oral mucosal exfoliation, stomatitis, glossodynia, dysgeusia, application site pain (GW Pharma, 2019)

SL vs BUC Physiology & Pharmacokinetics (Hua, 2019)

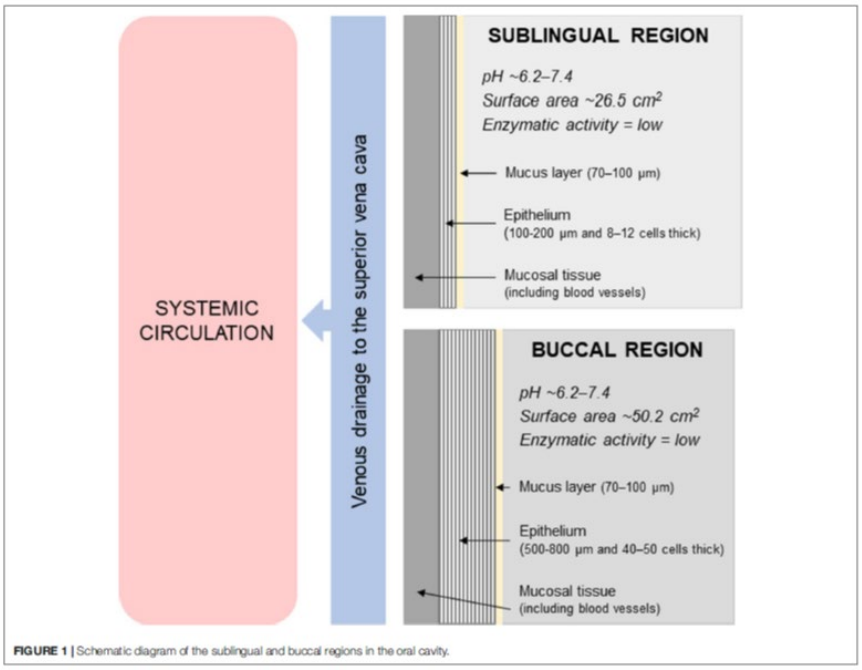

FIGURE 1 | Schematic diagram of the sublingual and buccal regions in the oral cavity.

Factors affecting SL and BUC absorption

Residence time of formulation – varies by formulation (spray, buccal film, SL tab, etc) and patient (ability to follow instructions not to chew or swallow the formulation and avoid eating/drinking for a period of time after use)

Drug absorption – balance of hydrophilic and lipophilic properties, low molecular weight, quality of mucosal tissue (absorption affected by inflammation, mouth ulcers, etc), concurrent cigarette smoking decreases absorption

Mouth environment - Saliva pH (ideally neutral pH can be altered by eating, drinking, oral disease); saliva amount excessive saliva or xerostomia impacts disintegration, dissolution of formulation

SL or BUC administration

- SL/BUC administration is an effective method for systemic absorption, especially for highly lipophilic medications. Cannabis extracts and individual preparations of THC and CBD are sufficiently lipophilic for this type of transmucosal absorption.
- SL/BUC administration bypasses first-pass liver metabolism. Extent of direct systemic absorption and bypass of first-pass effect is dependent on patient ability to hold SL/BUC medications in place for several minutes.
- If SL/BUC administered medications are swallowed prematurely, SL/BUC absorption is reduced, onset of therapeutic action will be delayed, and the route becomes a convenient method of oral administration for patients unable to swallow tablets or capsules.
- Onset of therapeutic action from SL/BUP administration is expected to be somewhat faster than with oral administration but slower than inhalation. Patient perception of faster onset of action with SL/BUC administration may provide benefit for patients who prefer not to use inhalation.

Key Findings

- Existing literature with supportive evidence is entirely based on GW Pharma (GWP) sponsored research completed as part of the international approval process for the commercially available (Canada, UK, Europe, Australia) nabiximols (Sativex®) oromucosal spray formulation – 25mg CBD-27mg THC/mL (0.1mL/spray actuation) and other dose-finding efficacy, safety and tolerability studies in healthy adult pharmacokinetic studies. (see evidence table comments GWP-sponsored supportive evidence provided by petition applicant).
- No evidence is available to support efficacy or safety of use of plant material for BUP/SL administration.
- Evidence supports systemic absorption of cannabis extracts via BUC/SL route of administration with pharmacokinetic parameters similar to oral dosing of cannabis extracts with the exception of a slight earlier time to peak. GWP-sponsored clinical trials methodologies involved careful instruction of patients/study subjects to maintain the SL/BUC spray in the mouth to increase dwelling time in contact with oromucosal tissue to enhance SL/BUC absorption. (Guy et al 2004; Karschner et al, 2011; Heustis, 2007).
- Evidence is equivocal for therapeutic benefit with BUC/SL ROA for to patients with trend towards benefit for spasticity related to multiple sclerosis (MS); other spasticity-related pain; urinary dysfunction related to bladder spasticity (not a QMC) and no effect or unknown effect for tremor (not a QMC), Parkinsons disease-related tremor or other neurological symptoms. (Koppel et al, 2014).
- GWP-sponsored studies demonstrated extensive inter-patient variability in pharmacokinetic parameters, including T_{max} (time to maximum concentration) and C_{max} (maximum concentration) after dosing but these studies provide limited explanation as to how inter-patient variability may impact patient therapeutic benefit.
- GWP-sponsored studies tend to group patients into a “responder” subset for additional therapeutic benefit analysis. Those patients that seemed to respond to SL/BUC administration of nabiximols as an adjuvant to managing pain from MS spasticity, cancer-related pain, or chemotherapy-induced neuropathic pain (CINP) continued nabiximols treatment and reported sustained benefits of pain control. (Portenoy et al, 2012; Lynch et al, 2014; Johnson et al, 2013; Rog et al, 2007; Langford et al, 2013).
- Evidence trends towards benefit with BUC/SL ROA for CINP, cancer-related pain in advanced illness, MS spasticity as adjuvant medication to usual opioid pain regimens when responding patients are allowed to self-titrate daily dosing and duration of benefit in responders does not seem to develop tolerance or require dose escalation. (Portenoy et al, 2012; Lynch et al, 2014; Johnson et al, 2013; Rog et al, 2007).
- Single porcine tissue absorption study for mucoadhesive tablet containing CBD only demonstrated permeation and accumulation (depot formation) of CBD in BUC mucosa with prolonged release into blood stream. (Itin et al, 2020).
- Adverse effects related to cannabis use – xerostomia, glossodynia, mouth ulceration, oral pain, oral discomfort, application site irritation, dysgeusia – are reported in the prescribing information for nabiximols (Sativex®) an oromucosal (BUC) spray. In all GWP-sponsored studies a high rate > 90% of patients/study subjects experienced

≥ 1 mild-moderate systemic adverse event (nausea, dizziness, tachycardia) in addition to the local oromucosal adverse effects. (GW Pharma, 2019; GWP sponsored studies)

- Xerostomia, periodontal disease, and dental caries are correlated with frequent use of cannabis products, although the literature generally refers to cannabis smoking or does not specify cannabis route of administration in these reports. (Le et al, 2019; Liu et al, 2020)

Recommendations

- Sufficient evidence is available to support medical/therapeutic use of cannabis extracts for systemic effect via oral mucosa using buccal or sublingual administration. No evidence supports use of cannabis extracts for local/topical effect (e.g., cancer treatment related oral mucositis). No evidence supports use of cannabis plant material for SL/BUC administration.
- Dispensaries and CTR physicians should provide clear patient/caregiver education and guidance on expected therapeutic effect for each SL or BUC product application as well as recommendation to disclose medical cannabis use to patient's dentist and oral surgeon.
- Avoid use of plant material for buccal or sublingual administration. All literature refers to use of cannabis for medical use via SL/BUC route as liquids (tinctures, oils), troches/lozenges, or film dosage forms.
- MMCP consider additional expert consultation with dentist and/or oral surgeon to confirm safety of application of cannabis extracts and product excipients (e.g., propylene glycol, ethanol, sorbitol, flavoring oils) to oral mucosa, either through repeated daily application or application of mucoadhesive films or tablets.

Evidence Review

Literature Provided by Petition Applicant			
Author	**Cite + PubMed Link**	**Title**	**Comment**
Portenoy et al	J Pain. 2012;13(5):438-449	Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial	*GWP sponsored*; 369 pt; No difference between nabiximols (2.7mgTHC/0.1mL-2.5mgCBD/0.1mL)/spray and placebo for 30% pain reduction overall, but sig improvements in responder subset for low (1-4 spray)/day and med (6-10 spray)/day dose; may have benefit as adjuvant to opioids in adv cancer pain
Lynch et al	J Pain Symptom Manage. 2014 Jan;47(1):166-73.	Double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain	No difference between nabiximols and placebo group for CINP; 18 pt; responder subset has CINP improvement
Johnson et al	J Pain Symptom Manage. 2013 Aug;46(2):207-18.	open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics	*GWP sponsored*; 43 pt; excluded pt with oral cancer or s/p oral radiotherapy; duration of use mean 25 day (range: 2d-579d); potential pain benefit as adjuvant to opioid therapy
Koppel et al	Neurology. 2014;82(17):1556-1563	Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology	Review of 34 studies; nabiximols, THC only, oral cannabis extract – probable benefit for MS, spasticity pain, urinary dysfunction, no benefit for tremor, PD, other neuro
Guy et al	J Cannabis Ther. 2004;3(3):35-77	Single Centre, Placebo-Controlled, Four Period, Crossover, Tolerability Study Assessing, Pharmacodynamic Effects, Pharmacokinetic Characteristics and Cognitive Profiles of a Single Dose of Three Formulations of Cannabis Based Medicine Extracts (CBMEs) (GWPD9901)	*GWP supported*; 20mgCBD:20mgTHC, high CBD only, high THC only single dose, healthy adults; PK parameters similar for BUC spray and SL drops; demonstrates extent/rate of absorption by SL/BU ROA
Guy et al	J Cannabis Ther. 2004;3(4):121-152	Phase I, Double Blind, Three-Way Crossover Study to Assess the Pharmacokinetic Profile of Cannabis Based Medicine Extract (CBME) Administered Sublingually in Variant Cannabinoid Ratios in Normal Healthy Male Volunteers (GWPK0215)	*GWP sponsored*; health adult dose finding PK study; THC only, CBD only, THC:CBD 10mg:10mg per dose mix; wide variety of PK parameters in 24 pts
Guy et al	J Cannabis Ther. 2004;3(4):79-120	Phase I, open label, four-way crossover study to compare the pharmacokinetic profiles of a single dose of 20 mg of a Cannabis Based Medicine Extract (CBME) Administered on 3	*GWP sponsored*; healthy adult dose admin to BUC area testing + oral cap CBME; no diff between oral & SL, BUC

		different areas of the buccal mucosa and to investigate the pharmacokinetics of CBME per Oral in Healthy Male and Female Volunteers (GWPK0112).	earlier Tmax; 10mgTHC:10mgCBD/dose=20mgCBME; 12 pts; establish BUC PK & safety
Karschner et al	Clin Chem. 2011 Jan;57(1):66-75	Plasma cannabinoid pharmacokinetics following controlled oral Δ9-tetrahydrocannabinol and oromucosal cannabis extract administration	*GWP sponsored*; 9 pt healthy adult; THC only vs nabiximols for PK with oromucosal vs PO ROA
Rog et al	Clin Ther. 2007 Sep;29(9):2068-79	Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial	*GWP sponsored*; long term (2 yr) tolerability-efficacy in MS pain; pt self titrate with 25mgCBD:27mgTHC/mL oromucosal spray (0.1mL/spray); 92% ≥ 1 AE; 25% withdrawal rate; stable dosing as adjuvant to usual pain meds
Langford et al	J Neurol. 2013 Apr;260(4):984-97	Double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis	*GWP sponsored*; 167 CBD-THC vs 172 placebo pt; pooled results into responders subset but no sig diff in active vs placebo for CNP reduction; self-titrated, high placebo response and AE rate; responders maintained response as adjuvant for CNP
Itin et al	Int J Pharm. 2020 May 15;581:119276. doi: 10.1016/j.ijpharm.2020.119276. Epub 2020 Mar 31	Prolonged oral transmucosal delivery of highly lipophilic drug cannabidiol	Animal (pig) study to determine permeation and accumulation of CBD only in oromucosal tissue with mucoadhesive tablet
Heustis MA	Chem Biodivers. 2007;4(8):1770-1884	Human Cannabinoid Pharmacokinetics	Review article on human cannabinoid PK various ROA; summarizes oromucosal info from GWP-sponsored studies

Additional Literature Reviewed by Protus

Author	Cite + PubMed Link	Title	Comment
Corroon et al	BMC Fam Pract . 2019 Dec 14;20(1):174	Indications and administration practices amongst medical cannabis healthcare providers: a cross-sectional survey	HCP survey results support patient preference for oral/oromucosal over inhalation delivery as a method of administration in general and for CBD predominant products
Hua S	Front Pharmacol. 2019; 10:1328	Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration	SL/BUC physiology and drug delivery characteristics
GW Pharma	Prescribing information	Nabiximols (Sativex®) product monograph.	Systemic and local adverse effects; SL or BUC mucosa application 25mg/mL CBD:27mg/mL THC in ethanol, propylene glycol, peppermint oil; PK info
Johal et al	Clin Med Insights Arthritis Musculoskelet Disord . 2020 Feb 19;13:1179544120906461.	Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis	Systemic and local adverse events related to oromucosal sprays reported; oromucosal clinical response for CNMP similar to oral ROA and similar absorption and bioavailability
Le et el	J Subst Use. 2019;24(1):61-65	Oral health implications of increased cannabis use among older adults: Another public health concern?	Dental caries, oral mucosa lesions from cannabis smoke exposure; xerostomia in adults > 65yoa
Lichtman et al	J Pain Symptom Manage . 2018 Feb;55(2):179-188	Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain	*GWP sponsored*; no benefit over placebo for cancer-related pain
Liu et al	Oral Dis. 2020 Oct;26(7):1366-1374	The effects of cannabis use on oral health	Review of potential effects of cannabis on oral health, primarily inhalation/smoking; recommend use disclosure to dental HCP
Cuba et al	J Clin Pharm Ther . 2017 Jun;42(3):245-250	Cannabidiol: an alternative therapeutic agent for oral mucositis?	Systematic review of CBD only preparations for topical application to oral mucosa to manage pain and inflammation of cancer treatment related oral mucositis based on animal studies and pharmacological mechanism; identifies potential but does not supply evidence to support use.

Prepared by Bridget McCrate Protus, PharmD, MLIS, BCGP, CDP bridget.protus@optum.com