Therapeutic Class Overview
Topical Lidocaine

INTRODUCTION

- Topical lidocaine is available as single entity and combination products (ie, lidocaine/prilocaine, lidocaine/hydrocortisone, lidocaine/tetracaine). These products are indicated for a number of conditions and are available in multiple dosage forms for topical use (ie, ointment, lotion, gel, cream, jelly, patch, solution) and as an oral solution.
- Lidocaine, prilocaine (amide-type local anesthetics) and tetracaine (ester local anesthetic) produce their analgesic effects through a reversible nerve conduction blockade by diminishing nerve membrane permeability to sodium. This action decreases the rate of membrane depolarization and increases the threshold for electrical excitability. The blockage affects all nerve fibers in the following sequence: autonomic, sensory and motor, with effects diminishing in reverse order. Loss of nerve function clinically is as follows: pain, temperature, touch, proprioception, skeletal muscle tone. Direct nerve membrane penetration is necessary for effective anesthesia (*Clinical Pharmacology 2020*).
- Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems; however, the rate and extent of absorption after topical administration is dependent on concentration, total dose, the site of application, and length of exposure. Following topical administration of ointment or jelly, peak effects typically occur within 3 to 5 minutes (*Clinical Pharmacology 2020)*.
- This review focuses on select topical lidocaine products that are available by prescription. Lidocaine products that are used parenterally are not included. Additionally, there are many topical lidocaine products that are available over the counter (OTC); however, the specific brands and availability of OTC products will not be included in this review. To note, many agents within this class have been used safely and effectively for many years; however, there are limited published data evaluating the efficacy of these products for their approved indications.
- Medispan class: Local Anesthetics – Topical and Topical Anesthetic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
lidocaine topical jelly 2%	✔
lidocaine topical gel 2%, 3%, 4%	✔
lidocaine lotion 3%**, 3.5%**	✔
lidocaine topical ointment 5%	✔
lidocaine oral viscous solution 2%	✔
lidocaine HCl topical solution 4%	✔
lidocaine HCl sterile solution 4%	✔
lidocaine topical cream 3%**, 3.25%**, 3.88%**, 4%**, 4.12%**	✔
lidocaine rectal cream 5%**	✔
lidocaine patch 5%	✔
lidocaine topical system 1.8%*	-
Combination Products	
lidocaine-prilocaine cream 2.5-2.5%**	✔
lidocaine-prilocaine cream 2.5-2.5% kits**	✔
lidocaine-prilocaine cream 2.5-2.5% & lidocaine gel 4% kit	✔
lidocaine-prilocaine cream 2.5-2.5% & lidocaine cream 3.88% kit†	-
lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit‡	-
lidocaine-hydrocortisone cream kit 2-2%**,3-0.5%**, 3-1%**, 3-2.5%**	✔

Drug	Generic Availability
lidocaine-hydrocortisone 2.8-0.55% with aloe gel kit**	✔
lidocaine-tetracaine cream 7-7%	✔

*only available as brand ZTlido
†only available as brand Prizotral
‡only available as brand Prilo Patch Kit
** Disclaimer: This drug has not been found by FDA to be safe and effective, and its labeling has not been approved by the FDA.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

Table 2. Indications for Single-Entity Products**

Single-Entity Products	Indication
lidocaine jelly	For prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)
lidocaine gel 2%	For the local management of skin wounds, including pressure ulcers, venous stasis ulcers, first and second degree burns, and superficial wounds and scrapes.
lidocaine gel 3%	For the relief of pain, soreness, abrasions, minor burns, insect bites and discomfort due to pruritus, pruritic eczemas, pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine gel 4%	For associated pain, painful wounds and wound healing in either open and closed injuries or conditions. Conditions of pain include topical pain, postsurgical pain and pain associated with various types of closed or open wounds. Conditions of closed wounds include soft tissue and bony injuries caused by contusions, hematomas, crush injuries and sprains/strains due to torsion, traction, compression and/or blunt trauma.
lidocaine lotion 3%	Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine lotion 3.5%	For use on normal intact skin for temporary relief of pain and itching due to minor cuts, minor scrapes, minor skin irritations, minor burns and insect bites
lidocaine ointment 5%	• For production of anesthesia of accessible mucous membranes of the oropharynx, • Anesthetic lubricant for intubation • For the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites.
lidocaine topical cream 3%, 3.88%, 4%, 4.12%	For the temporary relief of pain and itching associated with minor burns, sunburn, minor cuts, scrapes, insect bites, and minor skin irritation.
lidocaine topical cream 3.25%	For the relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness, and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine rectal cream 5%	Temporary relief of pain and itching due to anorectal disorders
lidocaine patch 5% lidocaine topical system 1.8%	For relief of pain associated with post-herpetic neuralgia (PHN).
lidocaine oral topical solution 2% viscous	For the production of topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx; for reducing gagging during the taking of x-ray pictures and dental impressions
lidocaine HCl sterile solution 4%	For the production of topical anesthesia of the mucous membranes of the respiratory tract or the genito-urinary tract
lidocaine HCl topical solution 4%	For the production of topical anesthesia of accessible mucous membranes of the

	oral and nasal cavities and proximal portions of the digestive tract.

** Disclaimer: Some products in this table (see Table 1) are not FDA-approved and have not had labeling approved by the FDA, but are available by prescription.

(*Prescribing Information: 2% Xylocaine viscous 2014, 4% Xylocaine-MPF 2010, 7T Lido gel 2018, Astero 2016, DermacinRx 2019, Gen7T 2019, Lido-K 2018, lidocaine ointment 5%, lidocaine HCl topical solution 2019, Lidoderm 2018, Lidodose 2018, Lidopin 2014, Lido Rx 2019, LMX4 2019, LMX 5 2018, PharmaPureRx lidocaine HCl 4.12% Cream 2019, Recticare 2019, ZTlido 2018)*

Table 3. Indications for Combination Products**

Combination Products	Indication
lidocaine-prilocaine cream 2.5-2.5%	Used as a topical anesthetic for use on: • Normal intact skin for local analgesia. • Genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.
lidocaine-prilocaine cream 2.5-2.5% kits	
lidocaine-prilocaine cream 2.5-2.5% & lidocaine gel 4% kit	
lidocaine-prilocaine cream 2.5-2.5% & lidocaine cream 3.88% kit	
lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit	
lidocaine-hydrocortisone cream kit	For the anti-inflammatory and anesthetic relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area.
lidocaine-tetracaine cream 7-7%	For use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.

** Disclaimer: Some products in this table (see Table 1) are not FDA-approved and have not had labeling approved by the FDA, but are available by prescription.

(Prescribing Information: Agoneaze 2018, Lido-BDK 2018, lidocaine HCl-hydrocortisone acetate cream 2018, lidocaine HCl-hydrocortisone acetate with aloe gel 2018, Nuvakaan 2019, Pliaglis 2019, Prilo Patch 2019, Prizotral 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Lidocaine/prilocaine has been studied as an anesthetic agent in several settings. Lidocaine products have not consistently shown improvements in pain scores compared to treatment with placebo (*Hopper et al 2014, Minassian et al 2002, Moppett et al 2004*).
  - Comparison of various lidocaine formulations to lidocaine/prilocaine creams has demonstrated that they have a similar anesthetic effect (*Herberger et al 2003*, *Koh et al 2004*).
  - In an open-label trial of 41 patients, lidocaine-prilocaine 2.5-2.5% cream was found to be significantly more effective than inhalation of a nitrous oxide-oxygen mixture in relieving pain associated with debridement of leg ulcers ($p < 0.001$) (*Claeys et al 2011*).
- Several clinical studies have evaluated the effectiveness of lidocaine-tetracaine cream as a topical anesthetic for many types of laser procedures including pulsed dye, leg vein, non-ablative, facial resurfacing, tattoo removal, and hair removal. Overall, similar results have been found, showing statistically better visual analog score (VAS) pain scores compared to placebo or head-to-head with other topical anesthetics (ie, lidocaine-prilocaine cream) (*Alster and Lupton 2002, Alster et al 2012, Bryan 2002, Chen et al 2003, Chen et al 2005, Doshi et al 2003, Jih et al 2004*).
- Lidocaine 5%

- A randomized, double-blind, placebo-controlled, 2-period crossover trial (N = 32) evaluated patients with PHN who were regular users of lidocaine 5% plaster from open-label extension studies. Patients were assigned to receive 14 days of lidocaine 5% plaster followed by 14 days of placebo or vice versa with no washout period. The primary endpoint was the “time to exit” where patients withdrew because their pain relief was 2 points lower than their normal response on a 6-point categorical verbal rating scale of pain relief (worse, no pain relief, slight relief, moderate relief, a lot of relief, and complete relief). The median time to exit was 14 days for lidocaine 5% plaster and 3.8 days for placebo ($p < 0.001$) (*Galer et al 1999*). In patients with PHN, treatment with lidocaine resulted in significant pain relief compared to placebo (*Galer et al 1999*, *Galer et al 2002*, *Meier et al 2003*). In addition, treatment with lidocaine was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999*, *Meier et al 2003*).
- The effectiveness of lidocaine patch 5% for the treatment of pain associated with PHN was demonstrated in a multi-center, open-label, phase 3 trial of up to 4 years duration. Patients applied up to 3 lidocaine 5% medicated plasters on the painful skin area for up to 12 hours a day. After 6 weeks, a mean pain relief of 4.3 ± 0.9 on a 6-point verbal-rating scale (1 = worse pain to 6 = complete relief) was reported and was maintained for the entire 12-month study and extension phase. The investigators' report for the global clinical impression of change was "very much improved" or "much improved" in about 80% of patients at each visit during the 12-month study. In the extension phase, the patient global impression of change was "very much" or "much" improved in 71% (49/69) at 24 months and 93% (40/43) at 36 months. In the safety population (n = 102) over the combined study period (4 years), drug-related adverse events included mainly administration site reactions: hypersensitivity (3.9%), pruritus (2.9%), irritation (2.9%), rash (2%), and skin reaction (1%) (*Sabatowski et al 2012*).
- A Cochrane systematic review of 12 small studies (N = 508) assessed the analgesic efficacy of topical lidocaine (5% patch, 5% cream, 5% gel, and 8% spray) vs placebo or active control for chronic neuropathic pain in adults. The limited information from single studies, mainly in PHN, indicated that topical lidocaine may be effective in treating neuropathic pain in a small number of patients and is well tolerated, at least in the short-term. There was no clear evidence of an effect on the incidence of adverse effects or withdrawals. However, the reviewers noted that the studies included ‘very low quality evidence’ and all had a ‘high risk of bias’ due to small size and incomplete outcome data (*Derry et al 2014*).
- In clinical studies, efficacy of the 5% lidocaine patch has consistently been reported to be superior to placebo and comparable or superior to oral pregabalin in patients with PHN pain or diabetic neuropathy (*Baron et al 2009a, Baron et al 2009b, Binder et al 2009, Rehm et al 2010, Rowbotham et al 1996*).

- Lidocaine topical system 1.8%
  - The approval of ZTlido (lidocaine topical system 1.8%) was based on trials that demonstrated the efficacy of *Lidoderm* for treatment of pain associated with PHN; no new clinical trials were required for FDA-approval (*The medical letter 2019*). In a single-dose, crossover study in 53 healthy volunteers, Ztlido 1.8% demonstrated equivalent exposure (area under the curve) and peak concentration of lidocaine to Lidoderm (*ZTlido prescribing information 2018*).

CLINICAL GUIDELINES

- Consensus guidelines for the use of topical anesthetics are lacking, therefore, decision making regarding the use of these agents is based on patient-specific factors and available comparative efficacy data.
  - The FDA recommends against using topical OTC medications for teething pain as some products may cause harm (*FDA Drug Safety* Communication *2018*).
  - The American Academy of Pediatrics (AAP) recommends managing teething pain with a chilled (not frozen) teething ring or gently rubbing/massaging with the caregiver's finger. Use of topical anesthetics for teething is discouraged by the AAP and American Academy of Pediatric Dentistry (AAPD) (*AAPD 2012).*
  - The 2010 European Federation of Neurological Societies (EFNS) guidelines on the pharmacological treatment of neuropathic pain suggest topical lidocaine may be considered first-line if there are concerns of adverse events with other oral medications in elderly patients who have PHN (*Attal et al 2010*).

SAFETY SUMMARY

- **Contraindications**
  - Hypersensitivity to any component of the formulation; hypersensitivity to another local anesthetic of the amide type.
- **Warnings**
  - *All drugs in class*
    - Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use.

- Overexposure: To avoid overexposure that could lead to adverse effects:
  - Do not use for longer duration or over larger surface areas than recommended.
  - Consider total amount of local anesthetics absorbed from all formulations.
  - Do not apply to mucous membranes or broken or inflamed skin.
  - Use with caution in patients who may be more sensitive to systemic effects, including acutely ill or debilitated patients, or those with severe hepatic disease or pseudocholinesterase deficiency.
- Risk of secondary exposure to children and pets: store and dispose out of reach of children and pets due to the risk of accidental exposure and resulting toxicity.
- Eye irritation: avoid contact with eyes

◦ *Oral topical lidocaine viscous solution*

- Boxed warning: Life-threatening and fatal events in infants and young children. There have been postmarketing cases of seizures, cardiopulmonary arrest, and death in patients < 3 years of age with use of lidocaine 2% viscous solution when it was not administered in strict adherence to the dosing and administration recommendations. Lidocaine 2% viscous solution should generally not be used for teething pain. For other conditions, the use of lidocaine 2% viscous solution in patients < 3 years of age should be limited to those situations where safer alternatives are not available or have been tried but failed. To decrease the risk of serious adverse events, caregivers should be instructed to strictly adhere to the prescribed dose and frequency of administration, and store the prescription bottle safely out of reach of children.

◦ *Lidocaine patch and topical system*

- The lidocaine patch is only recommended for use on intact skin.
- Placement of external heat sources, such as heating pads or electric blankets, over lidocaine patches is not recommended.

- **Key drug interactions**
  - Lidocaine and lidocaine-prilocaine cream should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.
- **Adverse events**
  - Lidocaine topical patch: application site reactions such as irritation, erythema, and pruritus.
  - Topical lidocaine and prilocaine: application site erythema (21% to 30%), application site pain, genital mucous membrane burning (17%).
  - Topical lidocaine and tetracaine: erythema (47%), skin discoloration (16%), and edema (14%).
  - Patients with severe hepatic impairment are at increased risk of developing lidocaine toxicity.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
lidocaine	Jelly 2%	Topical	Adults: No more than 30 mL (600 mg) in any 12-hour period according to the prescribing information	
lidocaine	Gel 2%, 3%, 4%	Topical	Apply to affected area ≤ 4 times daily as needed	
lidocaine	Lotion 3%, 3.5%, 4%	Topical	Apply a thin film to affected area 2 or 3 times daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
lidocaine	Ointment 5%	Topical	Adults: A single application not exceeding 5 g of ointment; maximum: 20 g per day.	
lidocaine	Viscous solution 2%	Topical	Adults: 15 mL orally no more frequently than every 3 hours; 8 doses per 24 hours. Pediatrics: ≥ 3 years of age: recommendations vary by age and weight. < 3 years of age: ≤ 1.2 mL (maximum: 4 doses per 12-hour period; use only if the underlying condition requires treatment with product volume of ≤ 1.2 mL)	Not approved for relief of teething pain and discomfort in infants and children; serious adverse (toxic) effects have been reported. Max: 4.5 mg/kg/dose (or 300 mg/dose).
lidocaine	Solution 4%	Topical	Adults: 1 to 5 mL (40 to 200 mg) per dose when used as a spray, applied with cotton applicators or packs, as when instilled into a cavity; maximum dose: 4.5 mg/kg, not to exceed 300 mg per dose Pediatrics: Dose varies with age and weight (maximum dose: 4.5 mg/kg)	
lidocaine	Cream 2%, 3%, 3.25%, 3.88%, 4%, 4.12%	Topical	Apply a thin film to the affected area 2 to 4 times daily for skin irritation.	
lidocaine	Rectal cream 5%	topical	Apply to affected area up to 6 times daily	
lidocaine	Topical system 1.8% Patch 5%	Topical	Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch(es) may remain in place for up to 12 hours in any 24-hour period.	Patches may be cut into smaller sizes with scissors prior to removal of the release liner
lidocaine-prilocaine	2.5-2.5% cream, 2.5-2.5% kit, 2.5-2.5% & 3.88% kit	Topical	Adults: A thick layer of lidocaine and prilocaine cream is applied to intact skin and covered with an occlusive dressing.	Should not be used in neonates with a gestational age less than 37 weeks nor in infants under

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				the age of 12 months who are receiving treatment with methemoglobin-inducing agents.
lidocaine-prilocaine and lidocaine	lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit	Topical	Cream: A thick layer of lidocaine and prilocaine cream is applied to intact skin and covered with an occlusive dressing. Patch: Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch(es) may remain in place for up to 12 hours in any 24-hour period.	Lidocaine and prilocaine cream should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of 12 months who are receiving treatment with methemoglobin-inducing agents
Lidocaine-hydro-cortisone	2-2%, 3-0.5%, 3-1%, 3-2.5%, 2.8-0.55% kits	Topical	Twice daily or as directed.	
Lidocaine-tetracaine	Cream 7-7%	Topical	Apply 20 to 30 minutes before procedure.	See full prescribing information for amount according to treatment site.

(*Drug Facts & Comparison 2020, Lexicomp Online 2020*)

See the current prescribing information for full details.

CONCLUSION

- Many of the topical lidocaine and lidocaine/prilocaine products are available generically and are available in different formulations including cream, ointment, jelly, gel, and as a topical patch.
- Lidocaine produces its analgesics effects through a reversible nerve conduction blockade by diminishing nerve membrane permeability to sodium.
- In general, adverse reactions associated with topical lidocaine are dose-related and may result from high plasma levels due to excessive dosage or rapid absorption, hypersensitivity, idiosyncrasy, or diminished tolerance. Common adverse reactions include localized skin reactions.
- Clinical evidence supporting the use of the lidocaine 5% patch in the treatment of PHN is limited due to the lack of comparative data to show clinical effectiveness.
  - A Cochrane review found no evidence from good quality randomized controlled studies to support the use of topical lidocaine to treat neuropathic pain, although individual studies indicated that it is effective for relief of pain (*Derry et al 2014*).
- The evidence to support the use of lidocaine 5% patch for other types of pain is uncertain due to the lack of available evidence as the clinical trials that were conducted had small sample sizes and a short follow-up period, leading to a high risk of bias. However, EFNS guidelines suggest lidocaine patches can be considered first line for elderly patients with PHN at high risk for severe adverse effects with oral medications.

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Publication Date: April 1, 2020