

Therapeutic Class Overview Scabicides and Pediculicides

INTRODUCTION

- Scabies and pediculosis are infestations of the skin caused by ectoparasites. Scabies is caused by the parasitic mite *Sarcoptes scabiei* and often results in an intense pruritic eruption and itching. Pediculi or lice can cause infestations either on the head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*), or the pubic region (*Phthirus pubis*). These skin conditions are common causes of skin rash and pruritus (Roos et al, 2001; Wendel et al, 2002). Head lice infestation crosses all social and geographic boundaries and generally affects children, primarily females, aged three to 12 years (Feldmeier, 2012). Scabies occur in both sexes, at all ages, and in all ethnic and socioeconomic groups; however, one epidemiologic study reported a higher prevalence in urban areas among women and children (Chosidow, 2006; Downs et al, 1999). The ideal agent for the treatment of head lice is one with high pediculicidal (capable of killing lice) and ovicidal (capable of killing eggs) activity with minimal toxicity (Villegas et al, 2012).
- The topical agents indicated for the management of scabies and head lice are listed in Table 1. All of the agents included in this review are Food and Drug Administration (FDA)-approved for the treatment of head lice with the exception of EURAX[®] (crotamiton), which is only indicated to treat scabies. Lindane lotion indicated to treat scabies has been discontinued; the shampoo is still available.
- The pediculicidal effects of most of these agents result from their neurotoxic effects on lice. These agents except benzyl alcohol cause periods of central nervous system hyperexcitation, resulting in paralysis and ultimately death of the lice. ULESFIA[®] (benzyl alcohol) is unique in that it disables the breathing structure of the lice, resulting in asphyxiation rather than neuroexcitation (ULESFIA prescribing information, 2015). Neurotoxic insecticides rely on the nervous system to exert their effect; therefore, newborn larvae are not susceptible to these agents since they do not develop a nervous system for several days after hatching. This presents a challenge for eliminating lice with a single treatment because the infestation typically includes lice from all stages of the life cycle, including newly hatched eggs.
- RID[®] (pyrethrins) and NIX[®] (permethrin) are pediculicidal, but not ovicidal, and therefore require nit combing and retreatment in seven to ten days to eradicate the infestation. Benzyl alcohol is not ovicidal and also requires a second treatment, but resistance is unlikely due to its unique mechanism of action. Malathion is both pediculicidal and ovicidal, but it is malodorous, requires 8 to 12 hours of application and is highly flammable. Lindane is neurotoxic and is not recommended as an initial treatment option (Lindane prescribing information, 2011). SKLICE[®] (ivermectin) and NATROBA[®] (spinosad) are pediculicidal but not ovicidal (NATROBA prescribing information, 2014). Topical ivermectin is approved as a single application product only (SKLICE prescribing information, 2016).
- Some data suggest a growing resistance to permethrin in the United States, with recent studies stating that the effectiveness of permethrin has declined to 25% and resistance to pyrethrins is widespread. (Koch et al, 2016, The Medical Letter, 2016). However, both the Centers for Disease Control and Prevention (CDC) as well as the American Academy of Pediatrics (AAP) continue to recommend permethrin as first-line antiparasitic therapy for treatment of both lice and scabies. For the treatment of head lice, therapy should be initiated with permethrin 1% or pyrethrins when resistance is not suspected. Malathion (in patients who are 6 years of age or older) and benzyl alcohol (in children older than 6 months) may be used when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. Per the AAP, spinosad and ivermectin might prove helpful in difficult cases, but the cost of these preparations should be taken into account by the prescriber. Lindane is no longer recommended by the AAP for use as treatment of head lice (Downs et al, 1999; CDC, 2015; CDC, 2016a; CDC, 2016b; Devore, Schultz, 2015).
- Medispan class: Scabicides and pediculicides and scabicide combinations



Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
EURAX (crotamiton)	Ranbaxy	07/06/1949	-
Lindane (gamma-hexachlorocyclohexane) <mark>*</mark>	various	1947	~
NATROBA (spinosad)	ParaPRO; Macoven	01/18/2011	~
OVIDE [®] (malathion)	various	08/02/1982	~
Permethrin* (ACTICIN [®] 5%, ELIMITE 5%, NIX [®] COMPLETE LICE SYSTEM [®] *, NIX CRÈME RINSE [®] *)	various	various	~
Piperonyl butoxide and pyrethrins [†] (LICIDE COMPLETE LICE TREATMENT KIT ^{®†} , PRONTO ^{®†} , RID ^{®†})	various	various	~
SKLICE (ivermectin)	Sanofi	02/07/2012	-
ULESFIA (benzyl alcohol)	Shionogi	04/09/2009	-

*Lindane shampoo is available; the lotion formulation has been discontinued.

Over-the-counter product is available in at least one dosage form or strength. Not all product options are listed as there are a number of over-the-counter options.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drugs	Scabies	Head Lice	Head and Pubic Lice	Head, Body, and Pubic Lice
EURAX (crotamiton)	~			
Lindane			✓ *	
Malathion		✓ †		
NATROBA (spinosad)		✓ ‡		
Permethrin	√ §∥	✓ ¶∥		
Piperonyl butoxide and pyrethrins				✔ **
SKLICE (ivermectin)		✓ ‡		
ULESFIA (benzyl alcohol)		✓ ‡		

*Lindane shampoo is reserved for patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of head or pubic lice.

+ In patients ≥6 years of age.

± In patients ≥6 months of age.

§ Permethrin cream is indicated for the treatment of scabies.

In patients ≥2 months of age

Permethrin lotion/cream rinse and liquid are indicated for the treatment of head lice.

**For pyrethrins, approved in patients ≥2 years of age.

(Prescribing information: EURAX, 2012; Lindane, 2011; NATROBA, 2014; OVIDE, 2013; SKLICE, 2016; ULESFIA, 2015; Clinical Pharmacology, 2017)

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

CLINICAL EFFICACY SUMMARY

Scabies

In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been reported with permethrin compared to crotamiton and lindane (Amer et al, 1992; Haustein et al, 1989; Schultz et al, 1990; Taplin et al, 1986b; Taplin et al, 1990; Zargari et al, 2006). In the largest study (N=467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin compared to lindane; however, the difference was not statistically significant (Schultz et al, 1990). In a single-blind, randomized controlled trial comparing ivermectin to crotamiton (N=340), two applications of ivermectin were as effective as a single application of crotamiton cream for the treatment of scabies at two weeks. After repeating therapy, ivermectin was superior to crotamiton cream at four weeks follow-up (Goldust et al, 2014).



• Both lindane and permethrin have also been compared to oral ivermectin for the treatment of scabies. Numerous studies have demonstrated a significantly lower cure rate after four weeks with lindane compared to oral ivermectin (Goldust et al, 2013; Madan et al, 2001; Mohebbipour et al, 2013). However, another study found similar efficacy between the two agents at day 15 and 29 after treatment (Chouela et al, 1999). Results from another study found that after a single application, permethrin was associated with a higher cure rate compared to ivermectin (Usha et al, 2000).

Lice

- Benzyl alcohol has been evaluated in two multicenter, randomized, double-blind, vehicle-controlled studies in patients (six months and older) with an active head lice infestation (N=628). In both studies, two applications of benzyl alcohol were associated with a significantly greater chance of treatment success (zero live lice 14 days following final treatment), compared to vehicle (P<0.001). The absolute difference in treatment success rates in study I was 71.4% in favor of benzyl alcohol (95% confidence interval [CI], 61.8 to 85.7%) and 48.8% (95% CI, 31.1 to 62%) in study II, again in favor of benzyl alcohol. In both studies, there was a lower incidence of treatment failure associated with benzyl alcohol compared to vehicle (3.3 vs 83.6% and 14.3 vs 60.7% in studies I and II, respectively; P<0.001 for both) (Meinking et al, 2010).
- Permethrin has demonstrated a higher rate of treatment success compared to lindane in the treatment of lice following a single application (Brandenburg et al, 1986; Bowerman et al, 1987; Kalter et al, 1987; Taplin et al, 1986a;). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (P>0.01) (Carson et al, 1988; DiNapoli et al, 1988). In multiple studies, malathion has been reported to be pediculicidal and ovicidal or had higher rates of cure when compared to permethrin (Meinking et al, 2004; Meinking et al, 2007; Roberts et al, 2000).
- Two identical, vehicle-controlled studies demonstrating the safety and efficacy of ivermectin lotion in the treatment of head lice were completed in 781 patients (six months and older) with head lice. The two studies showed that a higher percentage of patients treated with one application of ivermectin lotion, without nit combing, were treatment responders (free of live lice at day two and through day eight to the final evaluation at day 15) following a single application (combined study results for day 2: 94.9% vs 31.3%, respectively; day 8: 85.2% vs 20.8%, respectively; day 15: 73.8% vs 17.6%, respectively; P<0.001 for each comparison)(Pariser et al, 2012).
- Spinosad has been evaluated in two randomized, active-controlled trials of 1,038 patients aged six months or older with an active head lice infestation. Patients received spinosad without nit combing or permethrin 1% topical solution with nit combing. Fourteen days following treatment, the spinosad without nit combing treatment arm had a greater proportion of lice-free patients compared to permethrin with nit combing (P<0.001 for both trials). Moreover, the majority of patients treated with spinosad required only one course of treatment, compared to the majority of permethrin-treated patients who required two courses of treatment (P values not reported)(Stough et al, 2009).

SAFETY SUMMARY

- A boxed warning appears in the lindane labeling for the risk of neurologic toxicity including seizures and deaths. Lindane should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of scabies; the AAP no longer recommends lindane as a treatment of head lice (CDC, 2016a; Devore, Schultz, 2015).
- Lindane is contraindicated in patients with crusted (Norwegian) scabies and other skin conditions such as atopic dermatitis or psoriasis that may increase systemic absorption of the drug. Lindane is also contraindicated in premature infants because their scalps are more permeable and individuals with known uncontrolled seizure disorders.
- Malathion lotion is contraindicated for neonates and infants because their scalps are more permeable and may have increased absorption of malathion. Malathion lotion is flammable.
- All topical scabicide and pediculicide products are contraindicated in patients with a sensitivity or allergy to any active or inactive ingredient in the product.
- For the class, adverse events are mostly dermatological in nature.
- Drug interactions for this class are minimal due to the topical application. Consult the prescribing information for lindane regarding a list of drug interactions.

(Clinical Pharmacology, 2017)



DOSING AND ADMINISTRATION Table 3. Dosing and Administration

Pediatric Dose Availability Adult Dose Drug Scabies: EURAX Scabies: Cream: (crotamiton) Cream, lotion: prior to application, Use in children is off-label. The use of 10% (2 oz/tube) patients should bathe or shower. A thin crotamiton has been described layer of cream or lotion should be clinically, with the same directions as Lotion: thoroughly massaged into all skin for adults, in infants and children as 10% (2 oz/bottle, surfaces from the chin down to the toes young as 2 months of age, but 16 oz/bottle) including all skin folds and creases. treatment has been reported inferior to Crotamiton is left on the skin and a permethrin. However, due to treatment second application is advisable 24 failures, other agents appear to be hours later. The patient should take a preferred; crotamiton is considered an cleansing bath 48 hours after the last alternative agent. application to remove any remaining drug. The CDC does not recommend crotamiton for use in scabies. The use of lindane should be avoided Lindane Lice: Shampoo: Shampoo: apply a sufficient quantity of in infants and young children due to a 1% (2 oz/bottle) shampoo onto clean, dry hair; generally higher incidence of adverse reactions one ounce (30 mL) is sufficient, no in this age group. more than two ounces (60 mL) should be used. Work the shampoo into hair thoroughly and allow to remain on hair for four minutes. Add small quantities of water and massage until a good lather forms. Rinse thoroughly and towel dry briskly. Nits should be removed using a nit comb or tweezers. Retreatment is not recommended. NATROBA Lice: Lice: Topical Suspension: apply sufficient amount to Suspension: apply sufficient amount to Suspension: (spinosad) cover dry scalp, then apply to dry hair. cover dry scalp, then apply to dry hair. 0.9% (4 oz/bottle) Depending on hair length, apply up to Depending on hair length, apply up to 120 mL (one bottle) to adequately 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 cover scalp and hair. Leave on for 10 minutes, and then thoroughly rinse off minutes, and then thoroughly rinse off with warm water. If live lice are seen with warm water. If live lice are seen seven days following the first treatment, seven days following the first treatment. a second treatment should be applied. a second treatment should be applied. Approved for use in children six months of age or older.

Data as of March 14, 2017 YP-U/HI-U/ALS

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Drug	Adult Dose	Pediatric Dose	Availability
OVIDE (malathion)	<u>Head lice:</u> Lotion: apply to dry hair in an amount sufficient to thoroughly wet the hair and scalp. Allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered. After 8 to 12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs. If lice are still present after seven to nine days, repeat with a second application of lotion.	<u>Head lice:</u> Lotion: apply to dry hair in an amount sufficient to thoroughly wet the hair and scalp. Allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered. After 8 to 12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs. If lice are still present after seven to nine days, repeat with a second application of lotion. This should be used in children six years or older.	Lotion: 0.5% (2 oz/bottle)
Permethrin	Lice: Lotion: a sufficient volume (25 to 30 mL) applied to saturate the hair and scalp. A second application may be indicated if live lice are present seven days or more after initial application. Scabies: Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Remove cream by washing 8 to 14 hours after application. Repeat dose 7 to 14 days later if living mites are observed.	<u>Lice:</u> Lotion: a sufficient volume (25 to 30 mL) applied to saturate the hair and scalp. A second application may be indicated if live lice are present seven days or more after initial application. <u>Scabies:</u> Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Remove cream by washing 8 to 14 hours after application. Repeat dose 7 to 14 days later if living mites are observed. This should be used in children two months or older.	Cream: 5% (2 oz/tube) Lotion (crème rinse): 1% (2 oz/bottle; 1 and 2 bottles per package)
Piperonyl butoxide and pyrethrins	Lice: Solution: the undiluted liquid should be applied to dry hair and scalp or to any infested area until entirely wet. The liquid should not be used on the eyelashes or eyebrows. Shampoo: apply to the affected area until all hair is thoroughly wet and allowed to stand for no longer than 10 minutes. Then, the area should be washed with warm water and shampoo or soap. A fine-toothed comb, usually supplied with the product, should be used to remove dead lice and ova. The treatment should be repeated in 7 to 10 days to assure eradication of unhatched nits. Two consecutive applications should not be administered within 24 hours.	Lice: Solution: the undiluted liquid should be applied to dry hair and scalp or to any infested area until entirely wet. The liquid should not be used on the eyelashes or eyebrows. Shampoo: apply to the affected area until all hair is thoroughly wet and allowed to stand for no longer than 10 minutes. Then, the area should be washed with warm water and shampoo or soap. A fine-toothed comb, usually supplied with the product, should be used to remove dead lice and ova. The treatment should be repeated in 7 to 10 days to assure eradication of unhatched nits. Two consecutive applications should not be administered within 24 hours. This should be used in children two years or older.	Shampoo/ <mark>Solution</mark> : 4% piperonyl butoxide/0.33% pyrethrins (each kit)

Data as of March 14, 2017 YP-U/HI-U/ALS

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Drug	Adult Dose	Pediatric Dose	Availability
SKLICE (ivermectin)	Lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp. Leave lotion in place for 10 minutes and then rinse off with water.	Lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp. Leave lotion in place for 10 minutes and then rinse off with water.	Lotion: 0.5% (4 oz/tube)
		This should be used in children six months or older.	
ULESFIA (benzyl alcohol)	Lice: Lotion: apply sufficient lotion to dry hair to completely saturate the scalp; leave for 10 minutes, then rinse off with water; repeat treatment after seven days. Dosing is based on length of hair with ½ bottle to 6 bottles required.	Lice: Lotion: apply sufficient lotion to dry hair to completely saturate the scalp; leave for 10 minutes, then rinse off with water; repeat treatment after seven days. Dosing is based on length of hair with ½ bottle to 6 bottles required.	Lotion: 5% (two 8 ounce bottles per package)
	(Clinical J	This should be used in children six months or older.	
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SPECIAL POPULATIONS

Table 4. Special Populations **Population and Precaution** Drug Renal Hepatic Elderly **Pediatrics Pregnancy and Nursing*** Dysfunction Dysfunction EURAX Clinical studies did Not approved for Not studied in Not studied in Pregnancy Category C not include sufficient use in pediatric hepatic (crotamiton) renal numbers of subjects populations. dysfunction. Unknown whether dysfunction. excreted in breast milk: aged ≥65 years to use with caution. determine whether they respond differently from younger subjects. May be at greater Not studied in Not studied in Lindane Should not be Pregnancy Category C risk for serious hepatic used in very renal neurotoxicity. young children or dysfunction. dysfunction. Enters breast milk; use is premature infants contraindicated. Discard due to risk of milk for at least 24 hours seizures and after application. death. Use with caution in patients who weigh less than ~50 kg and especially in infants.

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	Population and Precaution				
Drug	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing*
NATROBA (spinosad)	Clinical studies did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects.	FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Not excreted into breast milk; use is recommended only if benefits outweigh the risks because it may be absorbed through the skin.
OVIDE (malathion)	No information	FDA-approved for use in children ≥6 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Permethrin	Safety and efficacy in elderly patients have not been established.	FDA-approved for use in children ≥2 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
Piperonyl butoxide and pyrethrins	Safety and efficacy in elderly patients have not been established.	FDA-approved for use in children ≥2 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Unknown whether excreted in breast milk; use with caution.
SKLICE (ivermectin)	Clinical studies did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects.	FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category C Following oral administration, it is excreted in human milk in low amounts; this has not been evaluated following topical administration.
ULESFIA (benzyl alcohol)	Safety and efficacy in elderly patients (>60 years) have not been established.	FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.

* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

(Clinical Pharmacology, 2017)

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CONCLUSIONS

- There are a number of effective topical scabicide and pediculicide agents available including EURAX (crotamiton), lindane, OVIDE (malathion), NATROBA (spinosad), NIX (permethrin), RID (piperonyl butoxide with pyrethrins), SKLICE (ivermectin) and ULESFIA (benzyl alcohol). Permethrin is recommended as first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States (Downs et al, 1999; CDC, 2016a; Devore, Schultz, 2015).
- Topical insecticides exert their pediculicidal and scabicidal effects through their neurotoxic actions on lice. Benzyl alcohol acts via asphyxiation of the parasite rather than neuroexcitation, theoretically lowering the risk of resistance. Ivermectin and spinosad are two newer agents approved for the treatment of head lice. Spinosad is not extensively metabolized, and therefore, it is still present and able to exert its effect when the lice eggs hatch and the nervous system develops. This may prevent the need for a second administration if no live lice are observed several days following the initial application (Villegas et al, 2012). Ivermectin has been approved for one-time use. Permethrin and the combination of pyrethrins and piperonyl butoxide are available over-the-counter (OTC) (CDC, 2016a). Lindane, a well-known older agent, is reserved as second-line therapy and carries a boxed warning describing risk of neurotoxicity associated with its use. Other available agents offer alternative options should a resistant case occur, or if a patient experiences treatment failure with an OTC product (CDC, 2016a; Devore, Schultz, 2015).
- Limited direct comparisons have been completed with agents in this class. Permethrin has demonstrated a higher rate of treatment success compared to lindane in the treatment of lice following a single application (Brandenburg et al, 1986; Bowerman et al, 1987; Taplin et al, 1986a). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (Carson et al, 1988; DiNapoli et al, 1988). Numerous studies have demonstrated a significantly lower cure rate after four weeks with lindane compared to oral ivermectin (Goldust et al, 2013; Madan et al, 2001; Mohebbipour et al, 2013); however one study found no difference at days 15 and 29 following treatments (Chouela et al, 1999). In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin (Meinking et al, 2004; Roberts et al, 2000).
- The newer agents, which include benzyl alcohol, ivermectin and spinosad, have shown cure rates (lice-free at day 14 or 15) of 75 to 76%, 71 to 76% and 84.6 to 86.7%, respectively, although there is limited published literature confirming these results.
- Overall, topical pediculicides are effective in eradicating head lice, but generally do not have any effect on ova (nits). The guidelines from CDC and AAP recommend permethrin or the combination of pyrethrins and piperonyl butoxide for head lice when resistance is not suspected (AAP Red Book, 2012; CDC, 2016a; Devore, Schultz, 2015). Retreatment of head lice usually is recommended because most approved pediculicides are not completely ovicidal. Spinosad and malathion are the only ovicidal medications for the treatment of head lice, but the need for re-treatment has been reported (CDC, 2016a). Lindane is no longer recommended by the AAP for use as treatment of head lice (Devore, Schultz, 2015).
- A comparison of the overall success rates for the topical scabicide products shows 89 to 100% success with
 permethrin, 65 to 92% with lindane, and 60 to 88% with EURAX. The CDC guidelines recommend permethrin as the
 drug of choice for the treatment of scabies; lindane is not recommended as a first-line therapy due to its toxicity, and it
 should be restricted to patients who have failed treatment with or cannot tolerate other medications that pose less risk
 (CDC, 2016b). For crusted scabies, oral ivermectin should be co-administered with a topical agent.
- The CDC recommends permethrin or the combination of piperonyl butoxide and pyrethrins as equivalent therapies for pediculosis pubis (CDC, 2015).

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