



Antiparasitics, Topical Therapeutic Class Review (TCR)

October 1, 2018

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Magellan Rx Management.

All requests for permission should be mailed to:

Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCReDitor@magellanhealth.com.

October 2018

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2018 Magellan Rx Management. All Rights Reserved.

MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indication(s)
Prescription		
benzyl alcohol (Ulesfia®) ¹	Lachlan	Age ≥ 6 months: Treatment of head lice
crotamiton (Eurax®, Crotan™) ^{2,3}	Ranbaxy, Marnel	Treatment of scabies Symptomatic treatment of pruritus
ivermectin (Sklice®) ⁴	Arbor	Age ≥ 6 months: Treatment of head lice
lindane* ⁵	generic	Treatment of head lice and ova Treatment of crab lice and ova
malathion (Ovide®) ⁶	generic, Taro	Age ≥ 6 years: Treatment of head lice and ova
permethrin 5% cream (Elimite®) ⁷	generic, Mylan	Treatment of scabies
spinosad (Natroba®) ⁸	generic, Parapro	Age ≥ 6 months: Treatment of head lice
Over-The-Counter (OTC)		
permethrin 1% lotion (Nix®) ⁹	generic, Insight Pharma	Treatment of head lice Prophylaxis during head lice epidemic
pyrethrins/piperonyl butoxide (RID®, Vanallice™) ¹⁰	generic, Bayer, GM	Treatment of head lice Treatment of body lice Treatment of crab lice

*Lindane is reserved for patients who cannot tolerate other approved therapies or have failed treatment with other approved therapies.

OVERVIEW

Head lice, or *Pediculus humanus capitis*, are a worldwide public health concern affecting persons of all ages and socioeconomic backgrounds. In the United States (US), it is most common among children 3 to 11 years old and accounts for 6 to 12 million annual infestations.^{11,12} Head lice infestations are not typically associated with morbidity, are not a sign of uncleanliness, and do not transmit systemic disease, although secondary methicillin-resistant *Staphylococcus aureus* (MRSA) or streptococcal infections may occur.^{13,14,15} Pediculosis is a source of social stigma and embarrassment and can prevent children with nits from attending school where a “no nit” policy is in place.¹⁶ Itching is the primary symptom of pediculosis, which results from an allergic reaction to the saliva lice inject during feeding.

The primary mode of head lice transmission is direct head-to-head contact. Lice crawl using adapted claws; they do not jump, hop, fly, or use pets as vectors. Once off the host, head lice only survive < 1 day at room temperature; their eggs become nonviable within a week.^{17,18} In the US, head lice affects all socioeconomic groups; there is less infestation among African Americans than other races, possibly due to a lack of adaptation of the lice claws to grasp specific shape and width hair shafts; hair length is not a factor.¹⁹ Treatment should be initiated only when there is a clear diagnosis with living lice.

Topical pediculicides, toxic to the louse central nervous system (CNS), are the initial treatment choice for treatment of head lice.²⁰ Safety is a concern with pediculicides, since the infestation itself presents

minimal risk to the host. The 2015 American Academy of Pediatrics (AAP) Head Lice Guidelines and AAP's 2018 Red Book Report of the Committee on Infectious Diseases recommend topical OTC permethrin 1% lotion or pyrethrins with piperonyl butoxide, which have good safety profiles, as first-line for head lice when resistance to these products is not suspected.²¹ When resistance to these agents is confirmed or treatment fails, which is not attributed to improper OTC use, the AAP recommends other pediculicides: malathion (Ovide) in children \geq 6 years old, benzyl alcohol (Ulesfia), ivermectin (Sklice), and spinosad (Natroba) in children \geq 6 months old. The cost of the preparations should be taken into account by the prescriber. Lindane is no longer recommended by the AAP due to concerns with neurotoxicity, rare severe seizures in children, low ovicidal activity, and worldwide reports of resistance.

In a 2012 policy statement on pesticide exposure in children, the AAP introduced recommendations to minimize pediatric pesticide exposure. The AAP advises against overuse of pediculicides and advocates proper application methods to reduce children's exposure. Common pesticides on AAP's list include permethrin, malathion, and lindane.²²

The 2015 AAP guidelines and AAP's 2018 Red Book recommend checking all household members for head lice.^{23,24} Those with live lice or nits within 1 centimeter of the scalp should be treated. The AAP also considers it prudent to prophylactically treat bedmates even if no live lice are found. The AAP does not recommend pediculicide sprays since the nits are unlikely to incubate and hatch at room temperature or survive off the scalp beyond 48 hours. Clothing, bedding, and towels that have come in contact with the infested person within 48 hours prior to treatment can be machine washed with hot water and dried in hot air cycles. Furniture and carpeting can be vacuumed to remove an infested person's hair with potentially viable eggs attached. Treatment of pets is not recommended, as they are not involved in the transmission of human head lice.

For treatment for *Pediculosis pubis*, or pubic or crab lice, the 2015 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines recommend permethrin 1% cream or pyrethrins with piperonyl butoxide (RID, Vanallice) as first-line despite growing resistance.²⁵ Malathion or oral ivermectin (Stromectol) are considered alternative regimens. Lindane is second-line due to toxicity. All sexual contacts should be treated at the same time to prevent cross reinfection. Per the AAP Red Book 2018 Report of the Committee on Infectious diseases, all pediculicides used to treat other types of louse infections are effective for treatment of pubic lice. However, only pyrethrins with piperonyl butoxide are FDA-approved. Clean clothing after treatment and retreatment for patients with head lice, are recommended. Topical pediculicides should be avoided for pubic lice infestation of eyelashes.

Causes of treatment failure in pediculosis or scabies include misdiagnosis, noncompliance, reinfestation, resistance, inadequate treatment, and lack of drug ovicidal or residual killing properties. Incorrect pediculicide application should be considered first when there is treatment failure. No currently available pediculicide is 100% ovicidal; resistance to permethrin, lindane, pyrethrins, and the United Kingdom formulation of malathion has been reported.^{26,27,28,29,30,31,32,33,34} However, the actual rates of resistance to specific products can vary by region and are not fully known. There are multiple mechanisms of resistance to various agents, such as target site insensitivity known as knockdown-type resistance (*kdr* type) mutations. These *kdr* mutations may predict resistance to pyrethrins and permethrin. Although presence of *kdr* type mutations alone may not predict clinical failure, their increasing frequency in head louse populations coincides with reports of product failure in controlled

trials. A study of *kdr* allele frequency in North American human head louse showed *kdr* type T917I (TI) increased to 99.6% from 2007 to 2009 in the US, whereas it was 88.4% from 1999 to 2009.³⁵ This increase in resistance is attributed to the extensive use of pyrethrin and permethrin-based pediculicides over many years. More recently, a 2016 report of *kdr* resistance that addressed deficiencies in the aforementioned study by several of the same authors reported that overall mean resistance was 98.3%. Data were obtained from 138 sites in 48 states and showed high levels of resistance regardless of population size or whether lice were found in a rural, suburban, metropolitan, or urban setting.³⁶ Resistance to benzyl alcohol (Ulesfia) is unlikely due to its mechanism of action, but as its therapeutic effects are directed at the louse and not the ovum, a full treatment course involves reapplication after 7 days to ensure eradication of hatched ova.^{37,38} Treatment failure should be suspected if live lice are still present 2 to 3 days after the second treatment of a product has been applied correctly, and no other cause of failure can be identified. Subsequent treatment should be with a different class.^{39,40} This should be followed by a second application 7 to 10 days later (except for single-use topical ivermectin).⁴¹ Using higher strengths of permethrin are not more efficacious.^{42,43}

In contrast to head lice and pubic lice, *Pediculosis corporis* (body lice) are vectors of disease. Treatment of body lice consists of improving hygiene and regular changes of clean clothes and bedding.^{44,45,46} Infested clothing can be decontaminated by washing in hot water (at least 130° F), by machine drying at hot temperatures, by dry cleaning, or sealing clothes in plastic bags for 2 weeks. Pediculicides typically are not needed if materials are laundered at least weekly. However, some people with significant body hair may require full-body treatment with a pediculicide, as lice and eggs may adhere to body hair. Pyrethrin with piperonyl butoxide is the only FDA-approved treatment for body lice.

Scabies is a major public health concern in many poor regions. Scabies is caused by an 8-legged obligate human parasitic mite *Sarcoptes scabiei* and results in intense pruritus, which is due to a delayed type-IV hypersensitivity reaction to the mite, its feces, and eggs. There is also a characteristic rash and distribution pattern. It can affect the entire body but, in adults, the head and neck are usually not affected. The female mite burrows under the skin and lays 10 to 25 eggs before dying. The eggs hatch in 3 days, leave the burrow for the skin surface, and mature into adults. Scabies can cause morbidity from secondary infections. If left untreated, staphylococcal infections including impetigo, ecthyma, paronychia, and furunculosis can occur.^{47,48} Transmission of scabies is usually from direct person-to-person contact. The mites can survive off a host for 24 to 36 hours and longer in colder temperatures.^{49,50} Crusted scabies or Norwegian scabies, an aggressive form of scabies, can occur in immunocompromised patients.

The 2015 CDC Sexually Transmitted Diseases (STD) Treatment Guidelines recommend topical permethrin 5% or oral ivermectin (off-label) as first-line for the treatment of scabies, despite resistance to permethrin.⁵¹ The CDC recommends lindane only as a second-line agent due to associated CNS toxicity and resistance. Crothamiton (Eurax, **Crotan**) is not mentioned in the CDC guidelines; however, it does have a role as an antipruritic in scabies. In the CDC's outline of treatments available for scabies, **crotamiton is noted as an FDA-approved option in adults with scabies.**⁵² Frequent treatment failure has been reported with crotamiton. All family members and close contacts must be prophylactically treated at the same time. Unlike head lice, environmental measures are essential for successful treatment of scabies, since mites can survive off the host. Clothes, linens, and towels must be washed with hot water and heat dried, dry-cleaned, or placed in a sealed plastic bag for at least 72 hours. **While the AAP Red Book 2018 Report of the Committee on Infectious diseases, recognize both topical**

permethrin 5% and oral ivermectin as effective agents for scabies treatment, they note that the scabies drug of choice is topical permethrin 5% cream, especially in pediatrics, pregnancy, and nursing women.⁵³ Off-label oral ivermectin should be considered in those who cannot tolerate or after treatment failure of topicals for scabies. Alternative drugs for scabies include crotamiton 10% cream or lotion. Lindane lotion is not recommended due to its poor safety and alternative options.

Systemic agents are used in the treatment of head lice, crab lice, and scabies, particularly in resistant cases. This review focuses on the available prescription topical antiparasitic treatments for head lice, crab lice, and scabies.

PHARMACOLOGY^{54,55,56,57,58,59,60,61,62}

The exact mechanism of crotamiton (Eurax, **Crotan**) is not known. It has scabicial activity against *Propionibacterium acnes* and *S. scabiei*, as well as antipruritic actions.

Benzyl alcohol (Ulesfia) is a topical pediculicide. It inhibits lice from closing their respiratory spiracles, which results in obstruction of the spiracles by the vehicle and subsequent asphyxiation of the lice. Benzyl alcohol does not have ovicidal activity; therefore, therapy must be repeated after 7 days.

Ivermectin (Sklice) is a member of the avermectin class and works primarily by binding selectively and with high affinity to glutamate-gated chloride channels. This leads to an increase in permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, and results in paralysis and death of the parasite. Avermectin selectivity is attributed to some mammals not having glutamate-gated chloride channels and the avermectins have a low affinity for mammalian ligand-gated chloride channels. In humans, ivermectin does not cross the blood-brain barrier.

Lindane is directly absorbed by parasites and their ova. It non-competitively inhibits gamma amino butyric acid (GABA) receptors. Lindane stimulates the nervous system, resulting in seizures and death of the parasites. Lindane resistance is thought to be via the GABA receptor becoming less sensitive to GABA antagonists.

Malathion (Ovide) is an organophosphate which acts as a pediculicide by inhibiting cholinesterase activity *in vivo*. Malathion resistance is thought to occur by increased levels of carboxylesterases that are involved in the drugs metabolism into non-malaxon intermediates.

Permethrin (Elimite, Nix) is a synthetic pyrethroid, which inhibits sodium ion influx through nerve cell membrane channels in ectoparasites, resulting in delayed repolarization and resultant paralysis and death of the parasites. Pyrethroid resistance is mediated by mutation of the alpha subunit gene of the neuronal voltage-gated sodium channel, conferring decreased sensitivity of the channel to pyrethroids. This is referred to as knock-down resistance.

The combination of pyrethrins/piperonyl butoxide (RID, **Vanallice**) blocks sodium channel repolarization of the arthropod neuron, leading to paralysis and death via the action of pyrethrin, and piperonyl butoxide inhibits the metabolism of pyrethrins in arthropods and diminishes pyrethrin resistance.

Spinosad (Natroba) is a topical pediculicide that works by central nervous system excitation and involuntary muscle contractions causing lice to become paralyzed and die. Although nit removal is not required, spinosad should be used in the context of an overall lice management program.

None of the pediculicides are 100% ovicidal.

PHARMACOKINETICS^{63,64,65,66,67,68,69,70,71,72}

Benzyl alcohol (Ulesfia) has shown systemic concentrations ranging from 1.97 to 2.99 mcg/mL 30 minutes post treatment and 1.63 mcg/mL 1 hour after treatment.

The degree of systemic absorption following topical administration of crotamiton (Eurax, **Crotan**) or malathion (Ovide) has not been determined, although the potential exists.

In a small pharmacokinetic study of 20 subjects ranging from 6 months to 3 years of age, after single application ivermectin (Sklice), the mean plasma concentration and area under the concentration-time curve from zero to time of last measurable concentration were 0.24 ± 0.23 ng/mL and 6.7 ± 11.2 ng/mL hr⁻¹, respectively.

Lindane acetone solution has shown a systemic absorption of up to 10%. Lindane is rapidly distributed followed by a longer beta-elimination phase. It is metabolized hepatically, excreted in the urine and feces, and has 4 major primary and 2 major secondary metabolites. Its half-life is about 18 hours.

Permethrin has a systemic absorption of 2% or less. It is metabolized by ester hydrolysis in the liver to inactive metabolites and is excreted primarily in the urine.

Percutaneous absorption of pyrethrins and piperonyl butoxide (RID, **Vanallice**) is minimal. Pyrethrins are, however, rapidly metabolized via hydrolysis and oxidation in the liver. The metabolites are primarily renally excreted.

In a small pharmacokinetic study, spinosad (Natroba) plasma levels were below the level of quantitation in all samples from 14 children.

CONTRAINDICATIONS/WARNINGS^{73,74,75,76,77,78,79,80,81,82,83}

Lindane is contraindicated in uncontrolled seizure disorders, crusted (Norwegian) scabies, or any condition which may increase systemic absorption (e.g., atopic dermatitis, psoriasis). It is also contraindicated in premature infants. Lindane carries a boxed warning, as its use may be associated with severe neurologic toxicities. Caution should be exercised in patients weighing less than 50 kg, particularly in infants, children, elderly, or patients with history of seizures, conditions which may increase risk of seizures, or taking medications, which may lower the seizure threshold.

Malathion (Ovide) is contraindicated in neonates and infants. Malathion labeling advises of the potential for second-degree chemical burns and stinging. Malathion lotion is flammable; avoidance of heat sources, including open flames and lighted cigarettes, is required.

Benzyl alcohol (Ulesfia) and spinosad (Natroba) should not be used in patients less than 6 months old. Neonates (less than 1 month old or preterm infants with a corrected age of less than 44 weeks) can be at risk for gasping syndrome if treated with benzyl alcohol lotion. Intravenous (IV) administration of products containing benzyl alcohol has been associated with neonatal gasping syndrome consisting of severe metabolic acidosis, gasping respirations, progressive hypotension, seizures, CNS depression, intraventricular hemorrhage, and death in preterm, low birth weight infants.

Ivermectin (Sklice) should not be used in patients less than 6 months of age. It should only be administered under adult supervision as accidental ingestion may occur in pediatric patients.

Permethrin (Elimite) is contraindicated in infants less than 2 months old. Treatment with permethrin may temporarily exacerbate symptoms of itching, redness, and swelling. Itching may occur even after

successful killing of lice. Rare cases of asthma exacerbations have been reported with use of pyrethroid-based products, such as permethrin in patients with ragweed or chrysanthemum allergies.⁸⁴

These agents are for external use only. Contact with face, eyes, and mucous membranes should be avoided. Acutely inflamed or raw skin should also not come into contact with these products.

Avoid fire, flame, smoking, and electric heat sources for hair (e.g., hair dryers) following use of malathion; it contains 78% isopropyl alcohol and is highly flammable.

DRUG INTERACTIONS^{85,86,87,88,89,90,91,92,93,94}

No drug interactions have been reported for crotamiton (Eurax, **Crotan**), ivermectin (Sklice), malathion (Ovide) permethrin (Elimite), pyrethrins/ piperonyl butoxide (RID, **Vanalice**), or spinosad (Natroba). Increased toxicity has been reported with the use of lindane and drugs which can lower seizure threshold. Oils, creams, or ointments may enhance lindane absorption; concomitant use should be avoided. Drug interaction studies were not conducted for benzyl alcohol (Ulesfia).

ADVERSE EFFECTS^{95,96,97,98,99,100,101,102,103}

Drug	Dermatitis	Pruritus/ Rash	Burning/ Stinging	Paresthesia	Erythema	Headache	Seizures
Prescription							
benzyl alcohol (Ulesfia)*	< 1	12 (pruritus) < 1 (rash)	< 1	< 1 [†]	10	nr	nr [‡]
crotamiton (Eurax, Crotan)	reported	reported	nr	nr	nr	nr	nr
ivermectin (Sklice) [§]	< 1	nr	< 1	nr	nr	nr	nr
lindane	reported	reported	nr	reported	nr	reported	reported
malathion (Ovide)	reported	nr	reported	nr	nr	nr	nr
permethrin 3% (Elimite)	nr	7 (pruritus) ≤ 2 (rash)	10	≤ 2	≤ 2	reported	nr
spinosad (Natroba)	nr	nr	nr	nr	3	nr	nr
Over-The-Counter (OTC)							
permethrin 1% (Nix)	nr	7 (pruritus) ≤ 2 (rash)	reported	nr	1-2	nr	nr
pyrethrins/piperonyl butoxide (RID, Vanalice)	nr	reported	nr	nr	reported	nr	nr

Adverse effects data are reported as percentages. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. nr = not reported

* Pyoderma and ocular irritation were reported in 7% and 6% of patients taking benzyl alcohol, respectively.

† Application site anesthesia and hypoesthesia were reported in 2% of patients using benzyl alcohol, respectively.

‡ IV products containing benzyl alcohol have been associated with neonatal gasping syndrome characterized by a number of symptoms including seizures.

§ Conjunctivitis, ocular hyperemia, and eye irritation were reported in less than 1% of patients taking ivermectin.

SPECIAL POPULATIONS^{104,105,106,107,108,109,110,111,112,113}

Pediatrics

Safety and effectiveness of benzyl alcohol (Ulesfia) have not been established in patients less than 6 months old.

Safety and effectiveness of ivermectin (Sklice) have not been established in patients less than 6 months old. There is potential for increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for immature skin barrier and risk of ivermectin toxicity.

Pyrethrin/piperonyl butoxide topicals (RID, Vanallice) should not be used in children less than 2 years old.

Safety and effectiveness of crotamiton (Eurax, Crotan) have not been established in pediatrics.

Extreme caution should be exercised for lindane in patients who weigh less than 50 kg, particularly in infants and children. The CDC does not recommend lindane use in children < 10 years old. It is also contraindicated in premature infants.

Safety and effectiveness of malathion (Ovide) have not been established in pediatrics younger than 6 years old; its use is contraindicated in neonates and infants.

Safety and effectiveness of OTC and prescription permethrin have not been established in patients less than 2 months old.

The safety and effectiveness of spinosad (Natroba) in patients less than 6 months of age have not been established.

Pregnancy

Crotamiton, lindane, and pyrethrins/piperonyl butoxide are classified as Pregnancy Category C. Benzyl alcohol, malathion, permethrin, and spinosad are Pregnancy Category B. Ivermectin was previously classified as Pregnancy Category C; however, its labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and now contains a description of the risk. There are no studies of ivermectin lotion use in pregnant women.

Hepatic Impairment

Lindane must be used with caution in patients with hepatic impairment.

Geriatrics

The safety of benzyl alcohol has not been established in patients over 60 years old.

Clinical studies with crotamiton did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between these patient groups, but greater sensitivity of some older individuals cannot be ruled out.

DOSAGES^{114,115,116,117,118,119,120,121,122,123,124}

Drug	Instructions	Availability
Prescription		
benzyl alcohol (Ulesfia)	Lice: Apply to dry hair and scalp; rinse after 10 minutes; repeat treatment in 7 days; usage guideline is based on hair length	5% lotion
crotamiton (Eurax, Crotan)	Scabies: Thoroughly massage into the skin of the whole body from the chin down, paying particular attention to all folds and creases; repeat in 24 hours; a cleansing bath should be taken 48 hours after final application Pruritus: Apply to affected areas as directed; repeat as needed	Eurax: 10% cream, lotion Crotan: 10% lotion
ivermectin (Sklice)	Lice: Apply to dry hair and scalp in an amount up to 1 tube to thoroughly coat hair and scalp; rinse after 10 minutes with water; do not retreat (for single application only)	0.5% lotion
lindane	Lice: Apply to clean, dry hair. Wait at least 1 hour after washing hair before applying lindane shampoo; do not retreat	1% shampoo
malathion (Ovide)	Lice: Apply once to dry hair as directed; rinse after 8 to 12 hours; repeat in 7 to 9 days if needed	0.5% lotion
permethrin (Elimite)	Scabies: Apply once from head to toe; rinse after 8 to 14 hours as directed; repeat in 14 days if live mites are present	5% cream
spinosad (Natroba)	Lice: Apply to cover dry scalp, then apply to dry hair; depending on hair length, apply up to 120 mL (1 bottle) to adequately cover scalp and hair; leave on for 10 minutes, then thoroughly rinse off spinosad with warm water; if live lice are seen 7 days after the first treatment, a second treatment should be applied	0.9% suspension
Over-The-Counter (OTC)		
permethrin (Nix)	Lice treatment: Apply to hair and scalp as directed; rinse after 10 minutes; if live lice are seen 7 days or more after the first application, a second treatment should be given Lice prophylaxis: Apply to hair and scalp as directed; rinse after 10 minutes; in epidemic settings, a second prophylactic application is recommended 2 weeks after the first application	1% lotion/1% creme rinse Nix Complete Kit contains 1% permethrin creme rinse, combing gel, lice comb, lice control spray
pyrethrins/piperonyl butoxide (RID, Vanallice)	Lice: Apply to dry hair and scalp or skin as directed; rinse after 10 minutes; repeat application once in 7 to 10 days Body Lice and Pubic Lice: Apply liberally to skin as directed; rinse after 10 minutes; repeat application once in 7 to 10 days	0.33%/4% shampoo, topical foam (RID) 0.3%/3.5% gel (Vanallice)

Previous recommendations have instructed patients to re-treat in 7 to 10 days with pyrethrins; however, some evidence based on the life cycle of lice suggests that re-treatment at day 9 is optimal. An alternate schedule of 3 treatments with non-ovicidal products on days 0, 7, and 13 to 15 has been proposed.¹²⁵

Before application of crotamiton, the affected skin should be thoroughly washed and loose scales scrubbed, rinsed, and towel dried.

Lindane shampoo should be applied to dry hair and massaged for 4 minutes; water is added gradually to create lather. Most patients will require 1 ounce of shampoo. Some patients may require 2 ounces of shampoo based on length and density of hair.

Nit combing is not required with spinosad but may assist with removal.¹²⁶

Most patients with scabies will require 1 ounce of permethrin 5% cream. Per the AAP Red Book 2018-2021 Report of the Committee on Infectious diseases, 2 or more applications (separated by a week) may be required to destroy all scabies mites.

These agents require application to the head, base of the neck, and behind the ears.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class, pediculosis capitis, pediculosis pubis, and scabies. Randomized controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are few well-designed studies for head lice; a number of the studies compare the topical agents to agents outside of this review, so they were not included. There are also few well-designed studies for scabies. A number of the studies compare the topical agents to oral therapy, so they were not included. There were no acceptable studies found for crab lice. Due to the lack of acceptable data, this evaluation includes studies performed versus permethrin 1% OTC (Nix), a lower strength than the prescription product included in this review. Open-label and pooled data were determined to be unacceptable. Many studies use the investigator-blinded design rather than using the double-blinded method and were included.

Only placebo-controlled trials are available for benzyl alcohol (Ulesfia) and ivermectin (Sklice). In patients \geq 6 months old, 14 days after the final treatment, 75% of patients on benzyl alcohol were lice-free versus 15% of vehicle.¹²⁷ Ivermectin lice free rates were 76.1% and 71.4% in the study arms compared to 16.2% and 18.9% with vehicle.^{128,129}

Head Lice

malathion (Ovide) and permethrin (Nix)

A randomized, investigator-blinded study of 66 children, mean age of 11.4 years old, with head lice compared malathion 0.5% lotion to permethrin 1% creme rinse.¹³⁰ Both agents were applied according

to label instructions, except malathion was applied for a reduced time of 20 minutes instead of the approved label of 8 to 12 hours. At day 8, patients still with live lice were retreated with the same agent they were initially treated with on day 1. Ovicidal and pediculicidal efficacy were evaluated on days 8 and 15. Treatment success was defined as being free of lice and viable eggs at day 15. Malathion was 98% pediculicidal and ovicidal versus 55% for permethrin at day 15 ($p < 0.0001$). At day 8, 50% less malathion patients required treatment versus the permethrin group. The reinfestation rate for malathion versus permethrin was 0% versus 33%, respectively.

malathion gel, malathion (Ovide) and permethrin (Nix)

A randomized, investigator-blinded, parallel-group, active-controlled study of 172 patients with head lice compared malathion 0.5% gel (30-, 60-, 90-minute applications), malathion 0.5% lotion (8- to 12-hour applications), and permethrin 1% creme rinse.¹³¹ Patients were treated on day 1 and re-evaluated on day 8; retreatment was done with the same product as given on day 1 if live lice were present. Cure was defined as absence of live lice on day 14. Using intention-to-treat, treatment success rates were 98% for the 30-minute malathion gel ($p < 0.0001$), 97% for malathion lotion ($p = 0.006$), and 45% for permethrin. Retreatment was highest for permethrin at 70%. Adverse events between treatment groups were not significantly different. Malathion gel is not commercially available in the U.S.

permethrin (Nix) and lindane

A randomized, single-blinded, multicenter study of 573 patients with head lice compared efficacy and tolerance of permethrin creme rinse 1% and lindane 1% shampoo.¹³² Both were applied according to the label: permethrin for 10 minutes and lindane for 4 minutes. At 14 days, 99% in the permethrin group were lice-free versus 85% of patients on lindane. This was statistically significant. Adverse events were mild and difficult to distinguish from infestation symptoms.

spinosad (Natroba) and permethrin (Nix)

Two multicenter, randomized, investigator-blind, active-controlled studies ($n = 1,038$) were conducted in patients 6 months of age and older with head lice infestation.^{133,134} Patients were randomized to spinosad 0.9% topical crème rinse or permethrin 1% crème rinse. For the evaluation of efficacy, the youngest subject from each household was considered to be the primary subject of the household, and other members in the household were enrolled in the study as secondary subjects, and evaluated for all safety parameters.

All patients who were treated on day 0 returned for efficacy evaluation at day 7. If live lice were present at day 7, they received a second treatment. Patients who were lice free on day 7 returned on day 14 for evaluation. Patients with live lice and who received a second treatment returned on days 14 and 21. Proportion of primary subjects who were free of live lice 14 days after the final treatment in the first study was 84.6% versus 44.9% for spinosad versus permethrin ($p < 0.001$). This efficacy measurement in the second study was 86.7% versus 42.9% for spinosad versus permethrin ($p < 0.001$). Few adverse events were reported, and were mild to moderate, including eye irritation (permethrin), ocular hyperemia, and application-site erythema/irritation (both medications).

Scabies

permethrin (Elimite) and crotamiton (Eurax)

Permethrin 5% cream was compared for effectiveness to crotamiton 10% cream for the treatment of scabies in a randomized, double-blinded study of 47 children between the ages of 2 months and 5 years.¹³⁵ Permethrin cured 30% of children versus 13% for crotamiton after 14 days. Four weeks after treatment, cure rates were 89% and 60%, respectively.

permethrin, lindane, and crotamiton (Eurax)

A randomized, parallel-group study of 150 patients with scabies compared permethrin 5% to lindane 1% and crotamiton 10%.¹³⁶ Patients were treated for 2 consecutive nights from neck to toe and then examined at various times for up to 4 weeks after the last treatment. Cure, defined as no new lesions and eradication of all original lesions, occurred in 98% of patients treated with permethrin, 88% of patients treated with crotamiton, and 84% treated with lindane. Cure rate was also highest among patients less than 10 years old with permethrin (100%) compared to crotamiton (80%) or lindane (0%). No adverse events were reported in any of the treatment groups.

META-ANALYSES

A Cochrane review of randomized trials of pediculicides found permethrin, synergized pyrethrin, and malathion effective in the treatment of lice.¹³⁷ The review found no evidence that any 1 pediculicide has greater effect than another. However, the emergence of resistance since these trials were conducted means there is no direct contemporary evidence of the comparative effectiveness of these products. The review emphasizes that the choice of therapy is dependent on local resistance patterns. The review also included studies utilizing physical methods and found them to be ineffective in treating head lice. Comparative studies with agents in this class support this finding.^{138,139} Adverse events reported were minor; however, the reporting quality varied among trials.

A Cochrane review of randomized trials of topical and systemic treatments for scabies found 20 small trials involving 2,392 patients.¹⁴⁰ Permethrin was more effective than oral ivermectin, crotamiton, and lindane. Permethrin also appeared more effective in reduction of itch persistence than either crotamiton or lindane.

SUMMARY

The American Academy of Pediatrics (AAP) Guidelines from 2015 and the **2018 AAP Red Book** continue to support a role for topical over-the-counter (OTC) permethrin and pyrethrins in the treatment of head lice, but resistance to these agents is increasing in the US and varies geographically. Recent studies of knockdown-type resistance alleles (*ldr* type) show an increased frequency of 98.3% to 99.6% resistance to human head louse in the US, regardless of population size or rural versus other environments. This increase is attributed to widespread use of pyrethrin and permethrin-based pediculicides. Local regional resistance patterns should be taken into consideration in pediculicide selection. Higher concentrations of permethrin or longer application times for the same agent kill few additional lice. Newer agents play a role when resistance to permethrin or pyrethrins is a concern or in treatment failure. For treatment failures not attributable to improper use of an OTC pediculicide, malathion lotion, benzyl alcohol lotion, ivermectin lotion, or spinosad suspension should be used.

Selection of agents should be made based on safety, efficacy, local resistance patterns, and patient age.

Malathion lotion is approved in ages ≥ 6 years of age. Caution should be used with malathion in order to prevent serious adverse events due to its high alcohol content; chemical burns with this agent have been reported. Lindane is no longer recommended for the treatment of head lice due to its poor safety and efficacy.

Benzyl alcohol (Ulesfia) has not been compared to other agents but has shown efficacy in head lice. Spinosad (Natroba) has shown better head lice eradication compared to topical permethrin but has not been compared to other prescription topical antiparasitics. Similar to benzyl alcohol (Ulesfia) topical lotion, spinosad topical suspension contains benzyl alcohol, which is associated with neonatal gasping syndrome. Spinosad and benzyl alcohol are approved for use in patients ≥ 6 months of age.

Ivermectin (Sklice) is a topical antiparasitic agent approved for patients ≥ 6 months of age. Studies revealed that ivermectin (Sklice) has better head lice eradication compared to placebo, but comparison to other prescription topical antiparasitics is not currently available.

For the treatment of scabies, prescription permethrin is the recommended topical agent.

REFERENCES

- 1 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 2 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 3 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.
- 4 Sklice [package insert]. Swiftwater, PA; Sanofi Pasteur; June 2017.
- 5 Lindane Shampoo [package insert]. Morton Grove, IL; Morton Grove; June 2010.
- 6 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 7 Elimite [package insert]. Newtown, PA; Prestium; August 2015.
- 8 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 9 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 10 Pyrethrins; Piperonyl Butoxide. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 11 Devore CD, Schutze GE for the Council on School health and Committee on Infectious Diseases. Clinical Report: Head Lice. Pediatrics. 2015; 135(5): e1355-65. DOI: 10.1542/peds.2015-0746. Available at: <http://pediatrics.aappublications.org/content/135/5/e1355>. Accessed September 30, 2018.
- 12 CDC. Head lice: epidemiology and risk factors. September 24, 2013. Available at: <http://www.cdc.gov/parasites/lice/head/epi.html>. Accessed September 30, 2018.
- 13 Devore CD, Schutze GE for the council on school health and committee on infectious diseases. Clinical report: Head lice. Pediatrics. 2015; 135(5): e1355-65. DOI: 10.1542/peds.2015-0746. Available at: <http://pediatrics.aappublications.org/content/135/5/e1355>. Accessed September 30, 2018.
- 14 Meinking TL. Infestations. Curr Probl Dermatol. 1999; 11:73-118.
- 15 Mumcuoglu KY, Klaus S, Kafka D, et al. Clinical observations related to head lice infestation. J Am Acad Dermatol. 1999; 25:248-251.
- 16 The National Pediculosis Association. Available at: <http://www.headlice.org/index.html>. Accessed September 30, 2018.
- 17 Roberts RJ. Clinical practice, head lice. N Engl J Med. 2002; 346(21):1645-1650.
- 18 AAP. Pediculosis Capitis. In: Kimberlin DW, Brady MT, Jackson MA, et al. Red Book: 2018 report of the committee on infectious diseases. 31st ed. Itasca, IL. American Academy of Pediatrics; 2018:607-612. Available at: <https://redbook.solutions.aap.org/book.aspx?bookid=2205>. Accessed December 20, 2018.
- 19 CDC. Head lice: epidemiology and risk factors. September 24, 2013. Available at: <http://www.cdc.gov/parasites/lice/head/epi.html>. Accessed September 30, 2018.
- 20 Flinders DC, De Schweintz P. Pediculosis and scabies. Am Fam Physician. 2004; 69(2):341-348.
- 21 Devore CD, Schutze GE for the council on school health and committee on infectious diseases. Clinical report: Head lice. Pediatrics. 2015; 135(5): e1355-65. DOI: 10.1542/peds.2015-0746. Available at: <http://pediatrics.aappublications.org/content/135/5/e1355>. Accessed September 30, 2018.
- 22 Pesticide Exposure in Children. American Academy of Pediatrics policy statement. Council on environmental health. Pediatrics. 2012; 130(6): e1757. DOI:10.1542/peds.2012-2757
- 23 Devore CD, Schutze GE for the council on school health and committee on infectious diseases. Clinical Report: Head lice. Pediatrics. 2015; 135(5): e1355-65. DOI: 10.1542/peds.2015-0746. Available at: <http://pediatrics.aappublications.org/content/135/5/e1355>. Accessed September 30, 2018.
- 24 AAP. Pediculosis Capitis. In: Kimberlin DW, Brady MT, Jackson MA, et al. Red Book: 2018 report of the committee on infectious diseases. 31st ed. Itasca, IL. American Academy of Pediatrics; 2018:607-612. Available at: <https://redbook.solutions.aap.org/book.aspx?bookid=2205>. Accessed December 20, 2018.
- 25 Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines 2015. Centers for Disease Control and Prevention. MMWR 2015; 64(RR-3):1-137. Available at: <http://www.cdc.gov/std/tg2015/tg-2015-print.pdf>. Accessed September 30, 2018.

- 26 Meinking TL, Serrano L, Hard B, et al. Comparative in vitro pediculicidal efficacy of treatments in a resistant head lice population in the United States. *Arch Dermatol*. 2002; 138(2):220-224.
- 27 Elston DM. Drugs used in the treatment of pediculosis. *J Drugs Dermatol*. 2005; 4(2):207-211.
- 28 Elston DM. What's eating you? *Pediculus humanus* (head louse and body louse). *Cutis*. 1999; 63(5):259-264.
- 29 Lebwohl M, Clark L, Levitt J. Therapy for head lice based on life cycle, resistance, and safety considerations. *Pediatrics*. 2007; 119(5):965-974.
- 30 Burkhart CG. Relationship of treatment-resistant head lice to the safety and efficacy of pediculicides. *Mayo Clin Proc*. 2004; 79(5):661-666.
- 31 Elston DM. Drugs used in the treatment of pediculosis. *J Drugs Dermatol*. 2005; 4(2):207-211.
- 32 Diamnatis SA, Morrell DS, Burkhart CN. Treatment of head lice. *Dermatol Ther*. 2009; 22(4):273-278.
- 33 Heymann WR. Head lice treatments; searching for the path of least resistance. *J Am Acad Dermatol*. 2009; 61(2):323-324.
- 34 Durand R, Bouvresse S, Berdjane Z, et al. Insecticide resistance in head lice: clinical, parasitological and genetic aspects. *Clin Microbiol Infect*. 2012; 18(4):338-344. DOI: 10.1111/j.1469-0691.2012.03806.x.
- 35 Yoon KS, Previte DJ, Hodgdon HE, et al. Knockdown allele resistance frequencies in North American head louse (*Anoplura: pediculidae*) populations. *J Med Entomol*; 2014; 51(2):450-457. Accessed February 20, 2017.
- 36 Gellatly KJ, Krim S, Palencha DJ, et al. Expansion of the Knockdown Resistance Frequency Map for Human Head Lice (Phthiraptera: Pediculidae) in the United States Using Quantitative Sequencing. *J Med Entomology*; 2016; 53(3): 653-659. DOI: 10.1093/jme/tjw023. Accessed February 20, 2017.
- 37 Benzyl alcohol lotion for head lice. *Med Lett Drugs Ther*. 2009; 51(1317).
- 38 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 39 Hansen RC. Overview: the state of head lice management and control. *Am J Manag Care*. 2004; 10(9):S260-263.
- 40 Wendell K, Rompalo A. Scabies and pediculosis pubis: an update of treatment regimens and general review. *Clin Infect Dis*. 2002; 35(Suppl 2):S146-151.
- 41 AAP. *Pediculosis Capitis*. In: Kimberlin DW, Brady MT, Jackson MA, et al. Red Book: 2018 report of the committee on infectious diseases. 31st ed. Itasca, IL. American Academy of Pediatrics; 2018:607-612. Available at: <https://redbook.solutions.aap.org/book.aspx?bookid=2205>. Accessed December 20, 2018.
- 42 Pollack RJ, Kiszewski A, Armstrong P, et al. Differential permethrin susceptibility of head lice sampled in the United States and Borneo. *Arch Pediatr Adolesc Med*. 1999; 153(9):969-973.
- 43 Downs AM, Stafford KA, Coles GC. Head lice: prevalence in schoolchildren and insecticide resistance. *Parasitol Today*. 1999; 15(1):1-4. Available at: <https://emedicine.medscape.com/article/2012115-overview>. Accessed October 4, 2018.
- 45 Available at: <https://www.cdc.gov/parasites/lice/body/treatment.html>. Accessed October 4, 2018.
- 46 AAP. *Pediculosis Corporis*. In: Kimberlin DW, Brady MT, Jackson MA, et al. Red Book: 2018 report of the committee on infectious diseases. 31st ed. Itasca, IL. American Academy of Pediatrics; 2018:612-613. Available at: <https://redbook.solutions.aap.org/book.aspx?bookid=2205>. Accessed December 20, 2018.
- 47 Roos TC, Alam M, Roos S, et al. Pharmacotherapy of ectoparasitic infections. *Drugs*. 2001; 61:1067-1088.
- 48 Heukelbach J, Feldmeier H. Scabies. *Lancet*. 2006; 367(9524):1767-1774.
- 49 Chosidow O. Clinical practices. Scabies. *N Engl J Med*. 2006; 354(16):1718-1727.
- 50 Arlian LG, Runyan RA, Achar S, et al. Survival and infectivity of *Sarcoptes scabiei* var. *canis* and var. *hominis*. *J Am Acad Dermatol*. 1984; 11:210-215.
- 51 Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines 2015. Centers for Disease Control and Prevention. *MMWR* 2015; 64(RR-3):1-137. Available at: <http://www.cdc.gov/std/tg2015/tg-2015-print.pdf>. Accessed September 30, 2018.
- 52 Centers for Disease Control and Prevention. Scabies. Resources for health professionals; medications. February 21, 2018. Available at: https://www.cdc.gov/parasites/scabies/health_professionals/meds.html. Accessed October 1, 2018.
- 53 AAP. *Pediculosis Pubis*. In: Kimberlin DW, Brady MT, Jackson MA, et al. Red Book: 2018 report of the committee on infectious diseases. 31st ed. Itasca, IL. American Academy of Pediatrics; 2018:613-614. Available at: <https://redbook.solutions.aap.org/book.aspx?bookid=2205>. Accessed December 20, 2018.
- 54 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 55 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.
- 56 Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 57 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 58 Elimate [package insert]. Newtown, PA; Prestium; August 2015.
- 59 Lebwohl M, Clark L, Levitt J. Therapy for head lice based on life cycle, resistance, and safety considerations. *Pediatrics*. 2007; 119(5):965-974.
- 60 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 61 *Pyrethrins; Piperonyl Butoxide*. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 62 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 63 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 64 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.
- 65 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 66 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 67 Lindane Shampoo [package insert]. Morton Grove, IL; Morton Grove; June 2010.
- 68 Elimate [package insert]. Newtown, PA; Prestium; August 2015.
- 69 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 70 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 71 *Pyrethrins; Piperonyl Butoxide*. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 72 Sklice [package insert]. Swiftwater, PA; Sanofi Pasteur; June 2017.
- 73 Lindane Shampoo [package insert]. Morton Grove, IL; Morton Grove; June 2010.
- 74 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 75 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.

- 76 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 77 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 78 Elimate [package insert]. Newtown, PA; Prestium: August 2015.
- 79 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 80 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 81 Sklice [package insert]. Swiftwater, PA; Sanofi Pasteur; June 2017.
- 82 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 83 **Pyrethrins; Piperonyl Butoxide**. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 84 Lebowitz M, Clark L, Levitt J. Therapy for head lice based on life cycle, resistance, and safety considerations. *Pediatrics*. 2007; 119(5):965-974.
- 85 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 86 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.
- 87 Lindane Shampoo [package insert]. Morton Grove, IL; Morton Grove; June 2010.
- 88 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 89 Elimate [package insert]. Newtown, PA; Prestium: August 2015.
- 90 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 91 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 92 Sklice [package insert]. Swiftwater, PA; Sanofi Pasteur; June 2017.
- 93 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 94 **Pyrethrins; Piperonyl Butoxide**. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 95 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 96 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.
- 97 Lindane Shampoo [package insert]. Morton Grove, IL; Morton Grove; June 2010.
- 98 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 99 Elimate [package insert]. Newtown, PA; Prestium: August 2015.
- 100 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 101 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 102 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 103 **Pyrethrins; Piperonyl Butoxide**. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 104 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 105 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.
- 106 Lindane Shampoo [package insert]. Morton Grove, IL; Morton Grove; June 2010.
- 107 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 108 Elimate [package insert]. Newtown, PA; Prestium: August 2015.
- 109 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 110 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 111 Sklice [package insert]. Swiftwater, PA; Sanofi Pasteur; June 2017.
- 112 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 113 **Pyrethrins; Piperonyl Butoxide**. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 114 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 115 Eurax [package insert]. Jacksonville, FL; Ranbaxy; September 2012.
- 116 Crotan. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6f7478fa-ed2b-4943-9d40-1fd0161a0854&type=display>. Accessed October 1, 2018.
- 117 Sklice [package insert]. Swiftwater, PA; Sanofi Pasteur; June 2017.
- 118 Lindane Shampoo [package insert]. Morton Grove, IL; Morton Grove; June 2010.
- 119 Ovide [package insert]. Hawthorne, NY; TaroPharma; March 2017.
- 120 Elimate [package insert]. Newtown, PA; Prestium: August 2015.
- 121 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 122 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 123 Permethrin 1%. Available at: www.clinicalpharmacology.com. Accessed September 30, 2018.
- 124 **Pyrethrins; Piperonyl Butoxide**. Available at: www.clinicalpharmacology.com. Accessed November 29, 2018.
- 125 Devore CD, Schutze GE for the council on school health and committee on infectious diseases. Clinical Report: Head Lice. *Pediatrics*. 2015; 135(5): e1355-65. DOI: 10.1542/peds.2015-0746. Available at: <http://pediatrics.aappublications.org/content/135/5/e1355>. Accessed September 30, 2018.
- 126 Stough D, Shellabarger S, Quiring J, et al. Efficacy and safety of spinosad and permethrin rinse for pediculosis capitis (head lice). *Pediatrics*. 2009; 124(3):e389-395.
- 127 Ulesfia [package insert]. Dublin, Ireland; Lachlan Pharmaceuticals; June 2015. Available at <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3dc60601-207d-4da8-9bd3-6f3f3577d231>. Accessed September 30, 2018.
- 128 Pariser DM, Meinking TL, Bell M, et al. Topical 0.5% ivermectin lotion for treatment of head lice. *N Engl J Med*. 2012 Nov;367(18):1687-93.
- 129 Sklice [package insert]. Swiftwater, PA; Sanofi Pasteur; June 2017.

-
- 130 Meinking TL, Vicaria M, Eyerdam DH, et al. Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared to Nix crème rinse (1% permethrin) for the treatment of head lice. *Pediatr Dermatol*. 2004; 21(6):670-674.
- 131 Meinking TL, Vicaria M, Eyerdam DH, et al. A randomized, investigator-blinded, time-ranging study of comparative efficacy of 0.5% malathion gel versus Ovide lotion (0.5% malathion) or Nix crème rinse (1% permethrin) used as labeled, for treatment of head lice. *Pediatr Dermatol*. 2007; 24(4):405-411.
- 132 Brandenburg K, Deinard AS, DiNapoli J, et al. 1% permethrin cream rinse vs. lindane shampoo in treating pediculosis capitis. *Am J Dis Child*. 1986; 140(9):894-896.
- 133 Stough D, Shellabarger S, Quiring J, et al. Efficacy and safety of spinosad and permethrin rinse for pediculosis capitis (head lice). *Pediatrics*. 2009; 124(3):e389-395.
- 134 Natroba [package insert]. Carmel, IN; Parapro; December 2014.
- 135 Taplin D, Meinking TL, Chen JA, et al. Comparison of crotamiton 10 % cream (Eurax) and permethrin 5% cream (Elimite) for the treatment of scabies in children. *Pediatr Dermatol*. 1990; 7(1):67-73.
- 136 Amer M, el-Gharib I. Permethrin versus crotamiton and lindane in the treatment of scabies. *Int J Dermatol*. 1992; 31(5):357-358.
- 137 Dodd CS. Withdrawn: interventions for treating headlice. *Cochrane Database Syst Rev*. 2007; (4):CD001165. Update of: *Cochrane Database Syst Rev*. 2001; (3):CD001165.
- 138 Roberts RJ, Casey D, Morgan DA, et al. Comparison of wet combing with malathion for treatment of head lice in the UK: a pragmatic randomized controlled trial. *Lancet*. 2000; 356(9229):540-544.
- 139 Meinking TL, Clineschmidt CM, Chen C, et al. An observer-blinded study of 1% permethrin creme rinse with and without adjunctive combing in patients with head lice. *J Pediatr*. 2002; 141(5):665-670.
- 140 Strong M, Johnstone PW. Interventions for treating scabies. *Cochrane Database Syst Rev*. 2007; (3):CD000320.