

## New Drug: *Ulesfia* (Benzyl Alcohol Lotion)

### What It Is

*Ulesfia* is a benzyl alcohol pediculicide lotion that was recently approved by the FDA for the topical treatment of head lice. This document discusses the appropriate use of *Ulesfia* and its place in therapy. A review of head lice treatment is also included.

### How It Works

*Ulesfia* does not have ovicidal activity. Rather, benzyl alcohol lotion inhibits lice from closing their respiratory spiracles which allows the product to penetrate lice, causing them to asphyxiate.<sup>1</sup>

### Indications

*Ulesfia* is indicated for the topical treatment of head lice infestation in patients six months of age or older.<sup>1</sup>

### How Supplied

*Ulesfia* is available as a 5% benzyl alcohol lotion. It is packaged in eight ounce bottles.<sup>1</sup> The AWP per bottle is \$30.

### Dosage

The amount of *Ulesfia* to be applied to the scalp and hair depends on the length of hair. *Ulesfia* should be applied to dry hair, using enough to saturate the scalp. It should be rinsed off with water ten minutes after application. The entire process should be repeated in seven days.<sup>1</sup>

The following table provides the amount of *Ulesfia* required based on hair length:<sup>1</sup>

Hair Length (inches)	Amount of <i>Ulesfia</i>
0-2	4 to 6 ounces
2-4	6 to 8 ounces
4-8	8 to 12 ounces
8-16	12 to 24 ounces
16-22	24 to 32 ounces
Over 22	32 to 48 ounces

It is important to note that *Ulesfia* is marketed in eight ounce bottles. In patients with longer hair, multiple bottles (i.e., up to six bottles) may be necessary for each treatment.

### Adverse Effects

The most common adverse effects noted in clinical trials include ocular irritation (6% versus 1% with placebo), application site irritation (2% versus 1% with placebo), and application site anesthesia and hypoesthesia (2% versus 0% with placebo). In a subset of patients who did not have pruritus prior to treatment, 12% of patients reported pruritus after treatment compared with 4% who received vehicle (placebo) only.<sup>1</sup>

Less common reactions (between 0.1% and 1% incidence) include application site dryness, excoriation, and dermatitis; paresthesia; thermal burn; dandruff; erythema; rash; and skin exfoliation.<sup>1</sup>

### Drug Interactions

Drug interaction studies were not performed with *Ulesfia*.<sup>1</sup>

### Contraindications

None.

### Precautions

Intravenous administration of benzyl alcohol to preterm, low birth weight neonates has resulted in neonatal gasping syndrome (severe metabolic acidosis, gasping respirations, progressive hypotension, seizures, central nervous system depression, intraventricular hemorrhage, death). Although it has not been studied, it is theoretically possible that preterm infants less than one month of age or preterm infants with a corrected gestational age of 44 weeks could be at risk of neonatal gasping syndrome with the topical use of *Ulesfia*.<sup>1</sup>

If benzyl alcohol lotion comes in contact with the eyes, eye irritation can occur. Eyes should

More . . .

immediately be flushed with water if the product gets in them.<sup>1</sup>

*Ulesfia* may cause allergic or irritant dermatitis.<sup>1</sup>

### **Use in Pregnancy**

*Ulesfia* is Pregnancy Category B. Well-controlled clinical trials of topical benzyl alcohol lotion have not been conducted in women who are pregnant. In animal studies (rabbit, rat), decreased fetal weight was noted in rabbits, when systemic benzyl alcohol was given at the highest dose.<sup>1</sup>

It is not known if benzyl alcohol is excreted in breast milk.<sup>1</sup>

### **Manufacturer**

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### **Commentary**

Head lice or *Pediculus capitis* is a worldwide concern affecting many children. While lice infestation is common and affects persons of all socioeconomic backgrounds and ages, it is most prevalent in children between the ages of three and 13.<sup>2</sup>

Lice transmission occurs through direct head-to-head contact as lice are not able to jump or fly. It is also stated to occur through the sharing of combs, hair brushes, or hats (particularly in the U.S. literature<sup>10,11</sup>), but supporting evidence is lacking.<sup>3</sup>

There are generally three basic options which have been scientifically evaluated for treatment of head lice.<sup>3-5</sup> These options include topical treatment (either pediculicides or suffocation-based therapy), wet combing, and oral therapy.<sup>3-5</sup>

The first-line treatment currently recommended is the over-the-counter product, 1% permethrin (*Nix*).<sup>4</sup> It has low toxicity, can be used in children as young as two months of age, and does not have cross-sensitivity with plant allergies, which is a theoretical risk with other agents like pyrethrins.<sup>1</sup> However, resistance to permethrin is well documented and may limit its usefulness.<sup>4-6</sup>

Other pediculicides commonly used include pyrethrins, lindane, and malathion. Pyrethrin (*A-*

*200*, *Licide*, *Pronto*, *RID*, others) is neurotoxic to lice, but has little toxicity in humans. It is not 100% ovicidal because newly laid eggs do not have a nervous system for several days and so a re-application may be required. Also this product may cause an allergic reaction in patients with ragweed sensitivity and can only be used in children two years of age or older.

Product labeling of most OTC products (permethrin, pyrethrins) used for lice recommend a second application at least seven to ten days after the initial application. However, recently the 7-day application time frame has been questioned.<sup>6,14</sup> The initial treatment of a pediculicide will kill living lice, but not affect all of the eggs. Under average conditions, an egg or nit will hatch in approximately 8.5 days.<sup>14</sup> Based on this time to hatch, by five to seven days after the initial treatment, 70% to 100% of the eggs or nits will not yet have hatched and a second treatment will not be effective. Consequently, some experts recommend a second treatment in nine to ten days.<sup>6,14,15</sup>

Lindane has many reports of resistance, and may have central nervous system side effects in humans. The FDA has also indicated this product should be used with caution in patients weighing less than 110 pounds. It is no longer considered a first-line agent, and should only be considered if head lice are unresponsive to other therapies.<sup>1</sup> In California, the use of lindane has been banned. For more information on the use of lindane, see our *Detail-Document*, FDA Issues Health Advisory Regarding Labeling Changes for Lindane Products.

Malathion, a prescription medication sold under the brand name of *Ovide* is effective for the treatment of lice in the U.S. It has high ovicidal activity, but the high alcohol content of commercial preparations makes risk of accidental ingestion and flammability a concern. For this reason it should be used with caution, and considered after other agents have been tried and are not effective. It is only approved for use in children six years of age and older. In addition, although resistance has not yet been proven in the U.S., extensive malathion-resistance to lice is common in England. Most experts think that with increased use in the U.S., resistance will become an issue in the U.S.<sup>2,5,7</sup>

More . . .

Other agents that have been tried include high concentration permethrin 5% (*Elimite*, *Actretin*, approved in the U.S. for the treatment of scabies), which does not appear to be effective in lice resistant to lower concentrations of permethrin.<sup>2,4</sup> The medication, crotamiton (*Eurax*), approved only for the treatment of scabies, has also been tried for head lice, but the safety in children has not been well studied.<sup>2,4</sup> The oral antibiotic sulfamethoxazole/trimethoprim (*Bactrim*, etc) has also been cited as being effective against head lice, but data are questionable.<sup>8,9</sup> Ivermectin is effective but should not be used in children less than 15 kg due to concerns about CNS toxicity.<sup>2,4</sup>

Most occlusive agents have not been clinically tested for efficacy, but may be commonly used.<sup>2,3</sup> Petrolatum is frequently used, but is difficult to remove. The National Pediculosis Association says most attempts to use *Vaseline* to try to smother lice are not successful.<sup>10</sup> Mayonnaise may serve as a growth medium for bacteria if not properly removed. There are conflicting reports about its efficacy as reported by the National Pediculosis Association.<sup>10</sup> *Cetaphil (Nuvo)* lotion has been studied in very limited trials. However, the trials demonstrating efficacy have a number of limitations including lack of a control group and the use of fine toothed “nit comb” to comb wet hair, a technique considered an effective treatment for head lice.<sup>3,11,12</sup>

Benzyl alcohol lotion or *Ulesfia* represents the first occlusive-based therapy for head lice approved by the FDA. Advantages of this product include the avoidance of pesticide use or neurotoxins, and the lack of resistance. Because benzyl alcohol suffocates the lice, resistance should not occur. In addition, it can be used in children as young as six months of age. As with other commonly used agents, it kills only lice, and not the nits, so a second application is necessary seven days after the initial applications. Disadvantages include topical irritant reactions and its cost compared with OTC pediculicides such as permethrin.

Approval of *Ulesfia* was based on a number of phase II and III clinical trials which are not published but are available in a formulary dossier from the manufacturer. In a phase II trial, 80 patients with head lice received either pyrethrin or *Ulesfia* either 5% or 10% applied as directed on the package labeling. A second dose of *Ulesfia*

was applied seven days later if live lice or nits were visible, while all patients treated with pyrethrin were given a second treatment (to comply with package labeling). Seven days after the second treatment, clinical success (defined as absence of live lice) was noted in 70% of patients treated with pyrethrin and both concentrations of *Ulesfia* compared with 52.6% in those treated with vehicle only. There was no significant difference between the treatment groups, although individual p values were not provided. In two phase III clinical trials evaluation of 250 patients with head lice, patients were treated with *Ulesfia* 5% according to product information. Using intention to treat analysis, *Ulesfia* 5% lotion was effective in 76.2% and 75% of patients compared with 4.8% and 26.2% with vehicle. The reasons for such divergent results with vehicle between the two studies were not provided. There are no other comparative clinical trials published in the literature.

In order to prove safety, the company conducted a bioavailability study in 20 children (six children between the ages of six months and three years, and 14 between the ages of four years and 11 years). Following a single application with enough lotion to fully saturate the scalp and hair, plasma concentrations of benzyl alcohol were measured. The majority of children had undetectable plasma benzyl alcohol concentrations. However, detectable concentrations were noted in three children in the younger cohort at 30 minutes after application (but no detectable levels at one, three, or six hours after application) and in one child in the older cohort at one hour after application (but no detectable levels upon subsequent monitoring).

Tea tree oil is another substance that is sometimes tried. Topically, tea tree oil can cause local irritation and inflammation, allergic contact eczema, and allergic contact dermatitis in some patients. It contains eucalyptol and limonene which may be responsible for the adverse effect of contact eczema. The use of tea tree oil is not recommended.<sup>10,13</sup>

Manual removal of nits is not necessary to prevent spread of lice after treatment with a pediculicide because only live lice can cause an infestation; however, many people prefer nit removal for aesthetic reasons.<sup>4</sup> Because available agents are not 100% ovicidal, most products and

More . . .

practitioners still recommend nit removal. Nit combs are fine-toothed and can make nit removal easier, but should not be used as sole therapy for lice infestation. Some people advocate the application of vinegar minutes before combing nits to loosen them, but this has not been proven to increase removal of nits.<sup>4</sup>

### Conclusion

Until additional research is performed, recommend the OTC preparations of permethrin. In cases where parents are concerned about the use of pediculicides, *Ulesfia* is an alternative. However, this agent may be significantly more expensive, especially when hair is longer and multiple bottles will be needed for each application. In cases resistant to OTC permethrin, malathion or *Ulesfia* may be considered. As with all therapies, these agents must be used according to the product information to maximize efficacy. Some experts feel that recurrence of lice is not due to resistance, but rather inappropriate use of medications used to treat lice. Nit removal combs can also be used as adjunctive therapy, to remove remaining lice and nits.

Parents and patients should be advised to avoid home remedies of occlusive agents. Parents should also understand proper household decontamination (cleaning items that the patient was in close contact with such as bedding, clothing, stuffed animals, etc. within the last 48 hours) to minimize reinfestation [Evidence Level C; consensus].<sup>4</sup>

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A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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