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SUBSPECIALIST CONSULT

Precocious Thelarche or Adrenarche

First recognize that a child with precocious puberty might actually have a serious underlying medical condition that triggers puberty. It is appropriate for you to distinguish true precocious

puberty from precocious puberty secondary to a general underlying medical condition if this is within your comfort zone. Begin with a complete history and physical examination. If you see physical signs of puberty that are not simply caused by “early puberty,” consider looking for underlying thyroid disorders, ovarian tumors, central nervous system tumors,

or even tumors of the adrenal gland. Importantly, perform a complete evaluation before initiation of any “treatment.” Occasionally, a patient with premature vaginal bleeding undergoes a very thorough hormone evaluation only to find the cause of her bleeding is a foreign body. Therefore, inspect the vaginal cavity as part of your physical examination or include this in your

gynecologist referral when a girl presents with vaginal bleeding and no other evident signs of puberty. You might spare the patient a full hormone work-up. Also refer the child to a gynecologist if you suspect an abnormality of the reproductive tract because of pelvic pain, vaginal discharge, and/or abnormal vaginal bleeding.

The treatment for precocious puberty is controversial itself. Administration of an injection that blocks gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus is the most commonly prescribed therapy (leuprolide acetate, Lupron Depot-PED). Consider referral of these patients because gynecologists and pediatric endocrinol-

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ogists have the most experience with this medication.

Other medications and lifestyle modifications are not particularly effective at halting early puberty.

Optimally, I advocate a combined effort among the pediatrician, the pediatric endocrinologist, and the gynecologist with a special interest in children.

Consider ordering a bone age study during your initial evaluation. It is an easy-to-order test for early puberty. Determination of the bone age of the left wrist is particularly worthwhile and provides useful information should you decide to refer to a specialist. Referral is warranted if a child with precocious puberty has advanced bone age.

Although precocious puberty includes thelarche and adrenarche, some important differences exist. Breast development, the growth spurt, and menses are all under the control of one system, the hypothalamic-pituitary-ovarian axis. Adrenarche, or secondary sexual hair, is primarily under the control of the adrenal gland, although the ovary is a major contributor to circulating androgens. Clinically, evaluate adrenal pathology more aggressively in cases of precocious adrenarche than in cases of thelarche.

It is also appropriate for a child without precocious puberty concerns to see a gynecologist in the early teenage years. This specialist can help you educate patients on reproductive health, including when Pap testing needs to be done and strategies to prevent pregnancy and sexually transmitted infection.

DR. MENON is a pediatric-adolescent gynecologist at Children’s Hospital of Wisconsin and assistant professor of obstetrics and gynecology at the Medical College of Wisconsin in Milwaukee. She said she had no conflicts of interest.

ALTABAX® (retapamulin ointment), 1%

The following is a brief summary only; see full prescribing information for complete product information.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Irritation

In the event of sensitization or severe local irritation from ALTABAX, usage should be discontinued, the ointment wiped off, and appropriate alternative therapy for the infection instituted [see Patient Counseling Information (17)].

5.2 Not for Systemic or Mucosal Use

ALTABAX is not intended for ingestion or for oral, intranasal, ophthalmic, or intravaginal use. ALTABAX has not been evaluated for use on mucosal surfaces [See Patient Counseling Information (17)]. Epistaxis has been reported with the use of ALTABAX on nasal mucosa.

5.3 Potential for Microbial Overgrowth

The use of antibiotics may promote the selection of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. Prescribing ALTABAX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The safety profile of ALTABAX was assessed in 2,115 adult and pediatric patients ≥9 months who used at least one dose from a 5-day, twice a day regimen of retapamulin ointment. Control groups included 819 adult and pediatric patients who used at least one dose of the active control (oral cephalixin), 172 patients who used an active topical comparator (not available in the US), and 71 patients who used placebo.

Adverse events rated by investigators as drug-related occurred in 5.5 % (116/2,115) of patients treated with retapamulin ointment, 6.6% (54/819) of patients receiving cephalixin, and 2.8% (2/71) of patients receiving placebo. The most common drug-related adverse events (≥1% of patients) were application site irritation (1.4%) in the retapamulin group, diarrhea (1.7%) in the cephalixin group, and application site pruritus (1.4%) and application site paresthesia (1.4%) in the placebo group.

Because clinical studies are conducted under varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Adults: The adverse events, regardless of attribution, reported in at least 1% of adults (18 years of age and older) who received ALTABAX are listed in Table 1.

Table 1. Adverse Events Reported by ≥1% of Adult Patients Treated With ALTABAX in Phase 3 Clinical Studies

Adverse Event	ALTABAX N = 1527 %	Cephalexin N = 698 %
Headache	2.0	2.0
Application site irritation	1.6	<1.0
Diarrhea	1.4	2.3
Nausea	1.2	1.9
Nasopharyngitis	1.2	<1.0
Creatinine phosphokinase increased	<1.0	1.0

Pediatrics: The adverse events, regardless of attribution, reported in at least 1% of pediatric patients aged 9 months to 17 years who received ALTABAX are listed in Table 2.

Table 2. Adverse Events Reported by ≥1% in Pediatric Patients Aged 9 Months to 17 Years Treated With ALTABAX in Phase 3 Clinical Studies

Adverse Event	ALTABAX N = 588 %	Cephalexin N = 121 %	Placebo N = 64 %
Application site pruritus	1.9	0	0
Diarrhea	1.7	5.0	0
Nasopharyngitis	1.5	1.7	0
Pruritus	1.5	1.0	1.6
Eczema	1.0	0	0
Headache	1.2	1.7	0
Pyrexia	1.2	<1.0	1.6

Other Adverse Events: Application site pain, erythema, and contact dermatitis were reported in less than 1% of patients in clinical studies.

7 DRUG INTERACTIONS

Co-administration of oral ketoconazole 200 mg twice daily increased retapamulin geometric mean AUC₀₋₂₄ and C_{max} by 81% after topical application of retapamulin ointment, 1% on the abraded skin of healthy adult males. Due to low systemic exposure to retapamulin following topical application in patients, dosage

BRIEF SUMMARY

adjustments for retapamulin are unnecessary when co-administered with CYP3A4 inhibitors, such as ketoconazole. Based on in vitro P450 inhibition studies and the low systemic exposure observed following topical application of ALTABAX, retapamulin is unlikely to affect the metabolism of other P450 substrates.

The effect of concurrent application of ALTABAX and other topical products to the same area of skin has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Effects on embryo-fetal development were assessed in pregnant rats given 50, 150, or 450 mg/kg/day by oral gavage on days 6 to 17 postcoitus. Maternal toxicity (decreased body weight gain and food consumption) and developmental toxicity (decreased fetal body weight and delayed skeletal ossification) were evident at doses ≥150 mg/kg/day. There were no treatment-related malformations observed in fetal rats.

Retapamulin was given as a continuous intravenous infusion to pregnant rabbits at dosages of 2.4, 7.2, or 24 mg/kg/day from day 7 to 19 of gestation. Maternal toxicity (decreased body weight gain, food consumption, and abortions) was demonstrated at dosages ≥7.2 mg/kg/day (8-fold the estimated maximum achievable human exposure, based on AUC, at 7.2 mg/kg/day). There was no treatment-related effect on embryo-fetal development.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALTABAX should be used in pregnancy only when the potential benefits outweigh the potential risk.

8.3 Nursing Mothers

It is not known whether retapamulin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALTABAX is administered to a nursing woman. The safe use of retapamulin during breast-feeding has not been established.

8.4 Pediatric Use

The safety and effectiveness of ALTABAX in the treatment of impetigo have been established in pediatric patients 9 months to 17 years of age. Use of ALTABAX in pediatric patients is supported by evidence from adequate and well-controlled studies of ALTABAX in which 588 pediatric patients received at least one dose of retapamulin ointment, 1% [see Adverse Reactions (6), Clinical Studies (14)]. The magnitude of efficacy and the safety profile of ALTABAX in pediatric patients 9 months and older were similar to those in adults.

The safety and effectiveness of ALTABAX in pediatric patients younger than 9 months of age have not been established.

8.5 Geriatric Use

Of the total number of patients in the adequate and well-controlled studies of ALTABAX, 234 patients were 65 years of age and older, of whom 114 patients were 75 years of age and older. No overall differences in effectiveness or safety were observed between these patients and younger adult patients.

10 OVERDOSAGE

Overdosage with ALTABAX has not been reported. Any signs or symptoms of overdose, either topically or by accidental ingestion, should be treated symptomatically consistent with good clinical practice.

There is no known antidote for overdoses of ALTABAX.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with retapamulin.

Retapamulin showed no genotoxicity when evaluated in vitro for gene mutation and/or chromosomal effects in the mouse lymphoma cell assay, in cultured human peripheral blood lymphocytes, or when evaluated in vivo in a rat micronucleus test.

No evidence of impaired fertility was found in male or female rats given retapamulin 50, 150, or 450 mg/kg/day orally.

17 PATIENT COUNSELING INFORMATION

Patients using ALTABAX and/or their guardians should receive the following information and instructions:

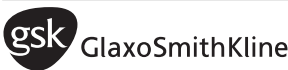
- Use ALTABAX as directed by the healthcare practitioner. As with any topical medication, patients and caregivers should wash their hands after application if the hands are not the area for treatment.
- ALTABAX is for external use only. Do not swallow ALTABAX or use it in the eyes, on the mouth or lips, inside the nose, or inside the female genital area.
- The treated area may be covered by a sterile bandage or gauze dressing, if desired. This may also be helpful for infants and young children who accidentally touch or lick the lesion site. A bandage will protect the treated area and avoid accidental transfer of ointment to the eyes or other areas.
- Use the medication for the full time recommended by the healthcare practitioner, even though symptoms may have improved.
- Notify the healthcare practitioner if there is no improvement in symptoms within 3 to 4 days after starting use of ALTABAX.
- ALTABAX may cause reactions at the site of application of the ointment. Inform the healthcare practitioner if the area of application worsens in irritation, redness, itching, burning, swelling, blistering, or oozing.

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