

An Overview of the Pediatric Medications for the Symptomatic Treatment of Allergic Rhinitis, Cough, and Cold

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ABSTRACT: Upper respiratory infections and allergic rhinitis are common diseases in children. In recent years, U.S. Food and Drug Administration has been promoting pediatric drug development with marketing exclusivity incentives and requirements. The assessment of clinical pharmacology, efficacy, and safety data has facilitated pediatric drug development and provided appropriate labeling for pediatric use. Regulatory decision making involves multiple evaluation processes, including drug exposure comparison between adult and pediatric population, formulation bridging, dose selection, and evaluation of efficacy and safety in pediatric patients. This article reviews the pediatric drugs indicated for cough, cold, and allergic rhinitis, focusing on the utility of clinical pharmacology, safety, and efficacy data in determining the pediatric dosing regimen and the approaches taken for regulatory decision making. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

Respiratory diseases are common in childhood. Among them, allergic rhinitis (AR) affects up to 50% of the pediatric population worldwide and 20–40 million people in the United States annually.^{1,2} If AR is not properly treated and becomes chronic, it can lead to complications in both upper and lower airways.³ Cough, an essential protective physiological mechanism that prevents food, liquid, dust, and chemicals from reaching the lower airways, is a symptom of many inflammatory diseases of the respiratory tract.⁴ It is generally associated with upper respiratory tract disorders in children.⁵ Over-the-counter (OTC)/nonprescription cough and cold medications have been used by patients for decades, and the pediatric cough and cold medications are widely used for the treatment of children's upper respiratory tract infections. In 2007, the Consumer Healthcare Products Association (CHPA) conducted a survey which indicated that 73% of 648 caregivers with children younger than 18 years of age had administered OTC cough and cold

medications. In response to the reports on the association of the OTC cough and cold products with serious adverse effects including death in young children, the Food and Drug Administration (FDA) held an advisory committee meeting discussing the safety concerns of cough and cold medicines for pediatric use in 2007.⁶ Because of serious adverse effects reported on the cough and cold medications, FDA issued a public health advisory to parents and caregivers, recommending not to use these medications in pediatrics less than 2 years in 2008.⁷ On October 8, 2008, FDA stated that FDA would support CHPA's announcement on nonprescription OTC cough and cold medicines in children and will not object to the new label modification stating "do not use in children under 4," which reflects a more restrictive use of the drugs in children.⁸

In recent years, the interest in pediatric pharmacology has grown significantly, leading to legislation in both the United States (Best Pharmaceuticals for Children Act 2002, Pediatric Research Equity Act 2003) and Europe (Pediatric Regulation 2007).^{9–12} These laws have resulted in improvements in pediatric dose determination, risk identification, and drug labeling. They also require pharmaceutical companies to develop appropriate pediatric formulations and conduct research in the full pediatric age range. The Food and Drug Administration Safety and Innovation Act of 2012 provided additional mandate to promote pediatric development for drugs and devices.

Clinical pharmacology plays a significant role in the pediatric research and drug development for the AR, cough, and cold drugs. This review provides an overview of some approaches used in the past for developing the AR, cough, and cold medications from a clinical pharmacology perspective. It covers 14 AR, cough, and cold drugs focusing on pharmacokinetics (PK), pharmacodynamics (PD), and dosing regimen selection. It also provides an overview of the pediatric clinical trial designs published for these 14 medications for AR, cough and cold

Abbreviations used: AR, allergic rhinitis; OTC, over-the-counter; FDA, Food and Drug Administration; CHPA, Consumer Healthcare Product Association; PK, pharmacokinetics; PD, pharmacodynamics; INS, intranasal corticosteroids; SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; HPA, hypothalamic–pituitary–adrenal; iTNSS, instant total nasal symptom score; rTNSS, reflective total nasal symptom score; BDP, beclomethasone dipropionate; NSAIDs, nonsteroidal anti-inflammatory drugs; AE, adverse event; PMR, Postmarketing Study Requirement; AQ, aqueous; QD, once daily; BID, twice daily; B, Best Pharmaceuticals for Children Act; P, Pediatric Research Equity Act; IBU, ibuprofen; PSE, pseudoephedrine; CPM, chlorpheniramine; NTE, not to exceed;

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indications. Regardless of the consistence to the current product development policies at regulatory agencies, the information discussed in this review is extracted from the available literature and product labeling. However, as science advances, it is important to stay informed of the most current policies for drug development with the regulatory agency.

Treatment of Allergic Rhinitis, Cough, and Cold Symptoms

The medications for AR, either seasonal (SAR), perennial (PAR),¹³ or both, have a significant impact on the quality of life, due to their adverse effects on sleep, cognition, and psychomotor function, etc.¹⁴ Currently available AR treatments include antihistamines (e.g., desloratadine, levocetirizine, loratadine, cetirizine, fexofenadine),¹⁵ intranasal corticosteroids (INSs) (e.g., fluticasone, ciclesonide, mometasone), subcutaneous immunotherapy,¹⁶ allergen injection immunotherapy,¹⁷ and antileukotrienes.¹⁸ Medications to treat cough and cold symptoms include antihistamines, antitussives, expectorants, and nasal decongestants. In addition to monotherapy, the OTC cough and cold preparations often combine two or more types of medications, including antihistamines, antitussives, expectorants, and decongestants. Sometimes, an antipyretics or analgesics such as acetaminophen or ibuprofen is incorporated in the combinations as well.

General Considerations for Drug Development in Pediatric Patients

Although appropriate pediatric clinical trial designs are still under discussion and evolving, the authors have presented the designs used and published for these products. Some of the clinical pharmacology issues related to pediatric trial designs were also discussed at the FDA clinical pharmacology advisory committee meeting in 2012.¹⁹

Most AR, cough, and cold drugs are administered orally or nasally. The dosing regimen in adults and pediatrics is summarized in Table 1, which shows that the approved dosing for most listed drugs for adolescents (12–17 years) is the same as that for adults whereas a reduced dose is generally given to children. Normally, the clinical study designs for dose selection in adolescents and adults are also the same for AR, cough and cold products. The focus of this review is on the study design in pediatric population younger than 12 years.

As compared to adults, pediatric patients have a relatively prolonged gastric emptying time, lower percentage of body fat, and a decreased amount of plasma protein.⁴² PK differences between adults and pediatric patients can be explained by the difference in body size and age. The ontogeny of metabolism for children younger than 6 years may also be a factor for the PK differences between adults and pediatric population.⁴³ The pediatric trial design is generally based on the prior PK and dosing regimen information from adult patients. Under the assumption that the pathophysiology, symptomatology, clinical course, and clinical treatment of AR are similar in pediatric and adult populations, the efficacy information in adults can be extrapolated to pediatric population.^{20,23,24,44}

For intranasal drug products, the systemic drug exposure is not consistently detectable or reliable as measures of local bioavailability and efficacy and may only provide information on systemic safety but not efficacy or local safety.⁴⁵ Therefore, the appropriate pediatrics dose should be determined mainly based on the efficacy and safety data.

The purpose for pediatric drug development is to obtain information in support of dosing, safety, and efficacy of medications in the pediatric population and communicate this information in the product labeling. The guidelines on the types of studies recommended for pediatric clinical trials are provided in the pediatric study decision tree.⁴⁶

For AR, cough, and cold indication, the list of key pediatric clinical studies is presented in Table 2. As summarized in the table, information from PK, efficacy, and safety data is generally used in assessing the effects of drugs in AR, cough, and cold patients.

The remainder of this review is organized according to the drug class (including individual drugs), with the aim to summarize various studies conducted for determining pediatric dosing during drug development in the treatment of AR, cough, and cold.

ANTIHISTAMINES

Oral and intranasal antihistamines are recommended as a first-line therapy for AR.⁶⁹ Although effective in relieving the symptoms of AR, first-generation antihistamines are associated with undesirable adverse effects, such as sedation and impairment of the psychomotor function. These side effects are caused by the lack of H₁ receptor selectivity and the penetration into the central nervous system of these drugs. Being more H₁ receptor specific, the second-generation antihistamines were developed with less frequent adverse effects observed with first-generation antihistamines.⁷⁰ Desloratadine, fexofenadine, levocetirizine, loratadine, cetirizine, and olopatadine belong to the second-generation antihistamines and are included in this category.

Oral Antihistamine

Desloratadine

The dose selection of desloratadine syrup in the pediatric population is based on a cross-study comparison of the plasma concentration of desloratadine in adults and pediatric subjects, established safety in pediatric patients and efficacy extrapolation from adult efficacy data to pediatric patients. The PK and safety of desloratadine were assessed in three safety studies and five PK studies.^{47–49} Following a single-dose administration of 2.5 and 1.25 mg of desloratadine syrup in 6–11-year-old subjects and 2–5-year-old subjects, respectively, the plasma concentration of desloratadine was similar to a single dose of 5 mg desloratadine tablet in adults. Population PK modeling and simulation analysis showed that doses of 1 and 1.25 mg in subjects aged 6–11 months and 12–23 months, respectively, are needed to obtain desloratadine plasma concentrations similar to those achieved in adults administered a single 5 mg dose of desloratadine syrup.^{20,47–49} The PK analysis also showed similar upper limit of exposure in children and adults who are poor metabolizers, but 6–7 times higher exposure than is seen in normal metabolizers. PK assessment demonstrated that the syrup and tablet formulations were bioequivalent following a single 5 mg oral dose.

Under the assumption that the course of seasonal and perennial AR and the effects of desloratadine are similar in the pediatric and adult populations, a similar plasma exposure should provide comparable efficacy in both populations. Under these

Table 1. FDA-Approved Allergy, Cough, and Cold Drugs

Generic Name	Brand Name	Indication	Age Range for Pediatric Patients	Adults and Adolescent Dosing Regimen (≥ 12 years)	Pediatrics Dosing Regimen (<12 years)
Desloratadine ^B	Clarinet ²⁰	SAR	≥ 2 years	One 5 mg tablet or RediTabs tablet QD or 2 teaspoonfuls (5 mg in 10 mL) syrup QD	1 teaspoonful (2.5 mg in 5 mL) syrup or one 2.5 mg RediTabs tablet QD (6–11 years); 1/2 teaspoonful (1.25 mg in 2.5 mL) syrup QD (12 months to 5 years);
Fexofenadine ^B	Allegra ²¹	SAR	≥ 2 years	60 mg BID or 180 mg QD (30 mg, 60 mg or 180 mg tablet)	2 mL (1.0 mg) syrup QD (6–11 months) 30 mg tablet, ODT or oral suspension BID (6–11 years);
Levocetirizine ^{B,P}	Xyzal ⁵⁴	SAR and PAR	≥ 6 months	5 mg QD in the evening (5 mg tablet or 2.5 mg/5 mL oral solution)	30 mg oral suspension BID (2–5 years) 2.5 mg QD in the evening (6–11 years); 1.25 mg (1/2 teaspoon oral solution [2.5 mL]) QD in the evening (6 months to 5 years)
Montelukast ^P	Singular ²³	SAR	≥ 2 years	One 10 mg tablet QD in the evening (≥ 15 years)	One 5 mg chewable tablet QD in the evening (6–14 years);
		PAR	≥ 6 months		One 4 mg chewable tablet or one packet of 4 mg oral granules QD in the evening (2–5 years); One packet of 4 mg oral granules QD in the evening (6–23 months)
Loratadine ^B	Claritin ²⁴	SAR	≥ 2 years	One 10 mg tablet or redivat, or 2 teaspoonfuls (10 mg) or syrup QD	One 10 mg tablet or redivat or 2 teaspoonfuls (10 mg) syrup QD (6–11 years);
Cetirizine ^B	Zyrtec ²⁵	SAR PAR	≥ 2 years ≥ 6 months	5 or 10 mg QD per day (5 or 10 mg tablet or 5 mg/mL syrup)	5 mg (1 teaspoonful) syrup QD (2–5 years) 5 or 10 mg (1 or 2 teaspoons) QD (6–11 years); 2.5 mg (1/2 teaspoon) QD (2–5 years); 2.5 mg (1/2 teaspoon) QD (6–23 months)
Olopatadine ^{B,P}	Patanase ²⁶	SAR	≥ 6 years	Two sprays per nostril (665 μ g per spray) BID	One spray per nostril (665 μ g per spray) BID (6–11 years)
Triamcinolone ^P	Nasacort AQ ²⁷	Nasal symptoms of SAR and PAR	≥ 2 years	Starting and maximum dose is 220 μ g QD (two sprays in each nostril), 55 μ g per spray	Starting dose is 110 μ g QD (one spray in each nostril), Maximum dose is 220 μ g QD (two sprays per nostril) (6–11 years)
Ciclesonide ^P	Omnaris ²⁸	Nasal symptoms of SAR	≥ 6 years	200 μ g QD administered as two sprays (50 μ g per spray) in each nostril	Starting and maximum dose 110 μ g QD (one spray in each nostril) (2–5 years) SAR: 200 μ g QD administered as two sprays (50 μ g per spray) in each nostril (6–11 years)
Mometasone ^P	Nasonex ²⁹	Nasal symptoms of AR, and nasal congestion associated with SAR	≥ 2 years	Two sprays (50 μ g per spray) in each nostril QD	One spray (50 μ g per spray) in each nostril QD

Continued

Table 1. Continued

Generic Name	Brand Name	Indication	Age Range for Pediatric Patients	Adults and Adolescent Dosing Regimen (≥ 12 years)	Pediatrics Dosing Regimen (< 12 years)
Ibuprofen ^B	Children's Advil ³⁰	Temporarily reduces fever, relieves minor aches and pains due to common cold, flu, sore throat, headaches, and toothaches	2–11 years	One 200 mg tablet every 4–6 h while symptoms persist, NTE six tablets in 24 h, unless directed by a doctor ³¹	2–3 years (24–35 lb): two 50 mg chewable tablets every 6–8 h, NTE four times a day 4–5 years (36–47 lb): three 50 mg chewable tablets every 6–8 h, NTE four times a day 6–8 years (48–59 lb): four 50 mg chewable tablets every 6–8 h, NTE four times a day 9–10 years (60–71 lb): five 50 mg chewable tablets every 6–8 h, NTE four times a day 11 years (72–95 lb): six 50 mg chewable tablets every 6–8 h, NTE four times a day 6–11 months (12–17 lb): 1.25 mL (50 mg/1.25 mL) suspension every 6–8 h, NTE four times a day 12–23 months (18–23 lb): 1.875 mL (50 mg/1.25 mL) suspension every 6–8 h, NTE four times a day
Ibuprofen ^B	Pediatric Advil ³²	Temporarily reduces fever, relieves minor aches and pain due to the common cold, flu, headaches, and toothaches	6–23 months	One 200 mg tablet every 4–6 h while symptoms persist, NTE six tablets in 24 h, unless directed by a doctor ³¹	6–11 months (12–17 lb): 1.25 mL (50 mg/1.25 mL) suspension every 6–8 h, NTE four times a day 12–23 months (18–23 lb): 1.875 mL (50 mg/1.25 mL) suspension every 6–8 h, NTE four times a day
Ibuprofen ^B	Children's Motrin ³³ Infant's Motrin ³⁵	Temporarily reduces fever, relieves minor aches and pains due to the common cold, flu, sore throat, headaches, and toothaches	2–3 years 6–23 months	One 200 mg tablet every 4–6 h while symptoms persist, NTE six caplets or tablets in 24 h, unless directed by a doctor ³⁴	6–11 months (12–17 lb): 1.25 mL (50 mg/1.25 mL) suspension every 6–8 h, NTE four times a day 12–23 months (18–23 lb): 1.875 mL (50 mg/1.25 mL) suspension every 6–8 h, NTE four times a day
Ibuprofen/ pseudoephedrine ^B	Children's Advil Cold ³⁶	Temporarily relieves these cold, sinus, and flu symptoms: nasal and sinus congestion, headache, stuffy nose, sore throat, minor aches and pains, fever	2–11 years	One caplet or capsule (200 mg/30 mg IBU/PSE) every 4–6 h, NTE six caplets in 24 h ^{37,38}	2–3 years (24–35 lb): 2.5 mL (50 mg/1.25 mL) suspension every 6–8 h, NTE four times a day 6–11 years (48–95 lb): two teaspoons (10 mL) (200 mg/30 mg IBU/PSE) suspension every 6 h, NTE four times a day 2–5 years (24–47 lb): one teaspoon (5 mL) (100 mg/15 mg IBU/PSE) suspension every 6 h, NTE four times a day 2–5 years (24–47 lb): one teaspoon (100 mg/15 mg IBU/PSE) suspension every 6 h, NTE four times a day 6–11 years (48–95 lb): two teaspoons (200 mg/30 mg IBU/PSE) suspension every 6 h, NTE four times a day 6–11 years (48–95 lb): two teaspoons (200 /30/2 mg IBU/PSE/CPM) suspension every 6 h, NTE four times a day
Ibuprofen/ pseudoephedrine ^B	Children's Motrin Cold ⁶⁸	Temporarily relieves these cold, sinus and flu symptoms: nasal and sinus congestion, stuffy nose, minor body aches and pains, headache, fever, sore throat	2–11 years	One caplet or capsule (200 mg/30 mg IBU/PSE) every 4–6 h, NTE six caplets in 24 h ^{37,38}	2–5 years (24–47 lb): one teaspoon (5 mL) (100 mg/15 mg IBU/PSE) suspension every 6 h, NTE four times a day 2–5 years (24–47 lb): one teaspoon (100 mg/15 mg IBU/PSE) suspension every 6 h, NTE four times a day 6–11 years (48–95 lb): two teaspoons (200 mg/30 mg IBU/PSE) suspension every 6 h, NTE four times a day 6–11 years (48–95 lb): two teaspoons (200 /30/2 mg IBU/PSE/CPM) suspension every 6 h, NTE four times a day
Ibuprofen/ chlorpheniramine/ pseudoephedrine ^P	Children's Advil Allergy Sinus ⁴⁰	Temporarily relieves symptoms associated with hay fever or other upper respiratory allergies and common cold runny nose; itchy, watery eyes; sneezing; headache, itching of the nose and throat, minor aches, and pains; nasal congestion; sinus pressure; fever	6–11 years	One caplet (200 /30/2 mg IBU/PSE/CPM) every 4–6 h, NTE six caplets in 24 h ⁴¹	6–11 years (48–95 lb): two teaspoons (200 /30/2 mg IBU/PSE/CPM) suspension every 6 h, NTE four times a day

Abbreviations: B: Best Pharmaceuticals for Children Act; P: Pediatric Research Equity Act; QD: once daily; BID: twice daily; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; IBU: ibuprofen; PSE: pseudoephedrine; CPM: chlorpheniramine; NTE: not to exceed

Table 2. Key Clinical Trials Used in Determining Allergy, Cough, and Cold Indication and Dosing Regimens Selection

Drug/Reference	Study Objectives and Design	No. Subjects; Age Range	Treatments	Key Results and Conclusions	Comments
Desloratadine NDA review 2004 ⁴⁷⁻⁴⁹	PK, safety; single-dose open label	<i>N</i> = 18; 2–5 years	Desloratadine 1.25 mg	PK exposure of 1.25 mg (2–5 years) and 2.5 mg (6–11 years) was comparable to that in adults received 5 mg dose of syrup or tablet	PK and safety data support the dosing in pediatrics 2–5 years of age at 1.25 mg, 6–11 years of age at 2.5 mg, 6–11 months of age at 1 mg, and 12–23 months of age at 1.25 mg
	PK, safety; single-dose open label	<i>N</i> = 18; 6–11 years	Desloratadine 2.5 mg		
	PK, safety; single-dose open label, parallel group	<i>N</i> = 58; 6–23 months	Desloratadine 0.625 mg (6–11 months), <i>N</i> = 10 Desloratadine 0.625 mg (12–23 months), <i>N</i> = 10 Desloratadine 1.25 mg (12–23 months), <i>N</i> = 19 Desloratadine 1.25 mg (6–11 months), <i>N</i> = 19	Population PK analysis showed that PK exposure of desloratadine 1 mg (6–11 months) and 1.25 mg (12–23 months) was comparable to that in adults who received 5 mg dose of syrup	
	Safety; randomized, parallel-group, double-blind	<i>N</i> = 111; 2–5 years	Desloratadine 1.25 mg/day 15 days, <i>N</i> = 55 Placebo 15 days, <i>N</i> = 56	The desloratadine was well tolerated. No serious AEs reported.	
	Safety; randomized, parallel-group, double-blind	<i>N</i> = 120; 6–11 years	Desloratadine 2.5 mg/day 15 days, <i>N</i> = 60 Placebo 15 days, <i>N</i> = 60		
	Safety; randomized, placebo-controlled, parallel-group, double-blind	<i>N</i> = 255; 6–23 months	Desloratadine 1.25 mg/day (12–23 months) 15 days, <i>N</i> = 66 Desloratadine 1 mg/day (6–11 months) 15 days, <i>N</i> = 65 Placebo 15 days, <i>N</i> = 124		
	PK, safety, and tolerability; single-dose, open label, multicenter	<i>N</i> = 50; 2–5 years	Fexofenadine 30 mg oral suspension	PK exposure was similar to the population PK analysis results obtained from adults data, no serious AEs or withdrawals due to AEs.	PK and safety data support the dosing in pediatrics 2–5 years of age at 30 mg
	Efficacy; randomized, placebo-controlled, double-blind, SAR patients	<i>N</i> = 411; 6–11 years	Fexofenadine 15, 30, and 60 mg BID, 2 weeks (tablet)	All three doses significantly reduced total symptom scores compared to placebo, and no dose response was seen. 60 mg BID did not provide any additional benefit over the 30 mg BID dosing.	Efficacy and safety data support the pediatric use at the dosing regimen at 30 mg BID 6–11 years of age
Fexofenadine NDA review 2006 ^{22,50}	PK, safety, and tolerability; single-dose, open label, multicenter	<i>N</i> = 50; 2–5 years	Fexofenadine 30 mg oral suspension	PK exposure was similar to the population PK analysis results obtained from adults data, no serious AEs or withdrawals due to AEs.	PK and safety data support the dosing in pediatrics 2–5 years of age at 30 mg
Allegra label ²¹	Efficacy; randomized, placebo-controlled, double-blind, SAR patients	<i>N</i> = 411; 6–11 years	Fexofenadine 15, 30, and 60 mg BID, 2 weeks (tablet)	All three doses significantly reduced total symptom scores compared to placebo, and no dose response was seen. 60 mg BID did not provide any additional benefit over the 30 mg BID dosing.	Efficacy and safety data support the pediatric use at the dosing regimen at 30 mg BID 6–11 years of age

Continued

Table 2. Continued

Drug/Reference	Study Objectives and Design	No. Subjects; Age Range	Treatments	Key Results and Conclusions	Comments
Levocetirizine Simons FE and Simon KJ, 2005 ⁵² NDA review 2007 ⁵³ Levocetirizine label ⁵⁴	PK, PD; single dose, open label	<i>N</i> = 14; 6–11 years	Levocetirizine 5 mg	PK exposure was two-fold increased compared to adults at 5 mg	PK data support dosing in pediatrics 6–11 years of age at 2.5 mg
	Safety; multicenter, randomized, double-blind, placebo-controlled, parallel-group	<i>N</i> = 69; 6–11 months	Levocetirizine 1.25 mg QD am (<i>N</i> = 45), 14 days; Placebo (<i>N</i> = 24), 14 days	AEs (such as somnolence and excitability) similar to that in placebo group	Safety data and results from population PK analysis support the pediatrics 6 months to 5 years of age dosing at 1.25 mg
NDA review 2009 ⁵⁵	Safety; multicenter, randomized, double-blind, placebo-controlled, parallel-group	<i>N</i> = 173; 1–5 years	Levocetirizine 1.25 mg BID (<i>N</i> = 114), 14 days; Placebo (<i>N</i> = 59), 14 days		
Montelukast Singular label ²³	Safety; multicenter, double blind, placebo-controlled, parallel-group	<i>N</i> = 280; 2–14 years	NA	Safety profile similar to placebo	Safety data support the pediatric dosing
Loratadine NDA supplement review package, 2000 ^{56,57}	PK, safety; single-dose, open label	<i>N</i> = 18; 2–5 years	5 mg loratadine	PK of loratadine and its metabolite desloratadine similar to adults at 10 mg dose	PK data support the pediatric dosing
	Safety; randomized, double blind, placebo-controlled, parallel group	<i>N</i> = 121; 2–5 years	5 mg loratadine QD (<i>N</i> = 60) 12 weeks; Placebo (<i>N</i> = 61), 12 weeks	No patients discontinued due to AEs	Safety data support the pediatric dosing

Continued

Table 2. Continued

Drug/Reference	Study Objectives and Design	No. Subjects; Age Range	Treatments	Key Results and Conclusions	Comments
Olopatadine					
NDA supplement review package, 2009 ⁵⁸	Efficacy, safety; multicenter, randomized, double-blind, vehicle-controlled, parallel group	<i>N</i> = 1188; 6–11 years	Olopatadine 0.6% one spray per nostril BID 2 weeks, <i>N</i> = 298 Vehicle one spray per nostril BID 2 weeks, <i>N</i> = 297 Olopatadine 0.4% two spray per nostril BID 2 weeks, <i>N</i> = 296 Vehicle two spray per nostril BID 2 weeks, <i>N</i> = 297 Olopatadine 0.4% one spray BID 14.5 days, <i>N</i> = 52 Olopatadine 0.6% one spray BID 14.5 days, <i>N</i> = 51 Olopatadine 0.6% two sprays BID 14.5 days, <i>N</i> = 52 Vehicle one spray BID 14.5 days, <i>N</i> = 51 Vehicle two sprays BID 14.5 days, <i>N</i> = 51	Change from baseline in rTNSS for both treatments significant improved compared to vehicle. The sponsor sought approval for the one spray dose.	Efficacy and safety data support pediatric dosing 0.6% one spray per nostril BID
	Safety, PK; randomized, vehicle-controlled, parallel group, multicenter	<i>N</i> = 257; 6–11 years		PK exposure at one spray similar to adults at dosing two sprays	PK and safety data support the pediatric dosing
Cetirizine					
NDA review package, 1998 ⁵⁹ , 2002 ⁴⁴	PK; single-dose, open label PK; single-dose, open label Efficacy, safety; placebo-controlled, double-blind, parallel group Safety; double-blind, placebo-controlled, multicenter PK; single-dose	<i>N</i> = 8; 2–6 years <i>N</i> = 8; 2–4 years <i>N</i> = 107; 2–6 years <i>N</i> = 96; 6–24 months <i>N</i> = 15; 6–24 months	5 mg cetirizine solution 5 mg cetirizine solution 5 mg cetirizine (10 mg/mL solution) QD 2 weeks, <i>N</i> = 54 Placebo, QD 2 weeks, <i>N</i> = 53 Cetirizine 0.25–0.75 mg/kg (4–11 mg/day) 7 days, <i>N</i> = 42 Placebo 7 days, <i>N</i> = 44 Cetirizine 0.25 mg/kg	Lower dose, e.g., 2.5 mg QD, should be proposed for pediatrics 2–5 years of age No safety issues raised, efficacy support claim of cetirizine in patients 2–6 years Cetirizine was well tolerated Population PK modeling and simulation demonstrated that 2.5 mg BID PK exposure was two-fold higher than that observed in adults given 10 mg QD	PK and safety data support the pediatric dosing 2–6 years of age PK and safety data support the pediatric dosing 6–24 months of age

Continued

Table 2. Continued

Drug/Reference	Study Objectives and Design	No. Subjects; Age Range	Treatments	Key Results and Conclusions	Comments
Triamcinolone NDA review Package 2008 ⁶⁰ ; Weinstein et al., 2009 ⁶¹	Safety and efficacy; randomized, double-blind, placebo-controlled	<i>N</i> = 474; 2–5 years	Triamcinolone AQ 110 µg QD in the morning (<i>N</i> = 236), placebo (<i>N</i> = 238) for 4 weeks, followed by 24 weeks open label treatment of triamcinolone AQ 110 µg QD in all patients (<i>N</i> = 474)	rTNSS significantly improved compared to placebo (<i>p</i> = 0.033, iTNSS had numerical trend favoring triamcinolone; No preferential discontinuations, 5% epistaxis observed in both treatment and placebo group, no nasal ulceration and nasal candidacies reported; limitations in HPA axis assessment	Efficacy and safety data support the pediatric dosing 2–5 years of age
	Knemometry; randomized, double-blind, placebo-controlled	<i>N</i> = 217; 2–5 years	Triamcinolone AQ 110 µg (<i>N</i> = 56) 2 weeks; Triamcinolone AQ 220 µg (<i>N</i> = 55) 2 weeks; Flonase 200 mcg (<i>N</i> = 51) 2 weeks	No clinically significant short-term effect on linear lower leg growth	HPA axis study was required to be conducted as a PMR
	PK, open label, multiple-dose	<i>N</i> = 15; 2–5 years	Placebo (<i>N</i> = 55) 2 weeks Triamcinolone AQ 110 µg QD (2–5 years, <i>N</i> = 15) 5 days Triamcinolone AQ 220 µg QD (adults, <i>N</i> = 15) 5 days	PK exposure in pediatrics 2–5 years of age is comparable to that in adults	
Nayak et al. 1998 ⁶²	HPA axis study; randomized, double-blind, parallel group	<i>N</i> = 80; 6–12 years	Triamcinolone AQ 220 µg (<i>N</i> = 28), 440 µg (<i>N</i> = 26), QD 6 weeks	No abnormal response to cosyntropin infusion	Safety and efficacy data support the pediatric dosing 6–11 years of age
Nasacort AQ nasal spray label ²⁷	Safety and efficacy; randomized, placebo-controlled, parallel group	<i>N</i> = 518; 6–12 years	Triamcinolone AQ 110 µg, 220 µg QD 2 and 12 weeks	Either dose resulted in statistically significant reductions in the severity of nasal symptoms of AR	
Ciclesonide NDA review package 2007 ⁶³	Safety and efficacy; double-blind, placebo-controlled, parallel group	<i>N</i> = 618; 6–11 years	Ciclesonide 200 µg QD (<i>N</i> = 215), 100 µg QD (<i>N</i> = 199), placebo (<i>N</i> = 204), 2 weeks	rTNSS statistically significantly improved from placebo for 200 µg QD (<i>p</i> = 0.04), whereas 100 µg QD did not (<i>p</i> = 0.103) in SAR patients	Efficacy and safety data support the dose 200 µg 6–11 years of age in SAR patients
	Safety and efficacy; double-blind, placebo-controlled, parallel group	<i>N</i> = 123; 2–5 years	Ciclesonide 200 µg QD (<i>N</i> = 81), placebo (<i>N</i> = 42) 12 weeks	Efficacy was not established	

Continued

Table 2. Continued

Drug/Reference	Study Objectives and Design	No. Subjects; Age Range	Treatments	Key Results and Conclusions	Comments
Mometasone Meltzer et al., 1999 ⁶⁴	Safety, efficacy; multicenter, double-blind, active and placebo-controlled, parallel group	<i>N</i> = 679; 6–11 years	Mometasone 25 µg/day (<i>N</i> = 137), 4 weeks Mometasone 100 µg/day (<i>N</i> = 135), 4 weeks Mometasone 200 µg/day (<i>N</i> = 133), 4 weeks BDP 84 µg (<i>N</i> = 138) 4 weeks Placebo (<i>N</i> = 136) 4 weeks	All doses of mometasone and beclomethasone significantly more effective in reducing total nasal symptom scores than placebo (<i>p</i> < 0.02). Mometasone 25 µg/day was less effective than other treatment (<i>p</i> < 0.05); mometasone 200 µg daily offered no additional effectiveness compared with 100 µg daily.	Efficacy and safety data support the dose of 100 µg/day in pediatrics 6–11 years of age.
Dibildox, 2001 ⁶⁵	Safety, efficacy; double-blind, placebo-controlled, with open label extension	<i>N</i> = 381; 3–11 years	Mometasone 100 mcg/day (<i>N</i> = 190), Placebo (<i>N</i> = 191) 4 weeks, with 100 mcg/day (<i>N</i> = 357) 6 months extension	TNSS in mometasone group decreased significantly greater than that in placebo group (<i>p</i> < 0.02)	
Ibuprofen/pseudoephedrine, Children's Advil Cold NDA review package 2002 ^{66,67}	PK; single-dose, randomized, open label, cross over	<i>N</i> = 28; 6–11 years	IBU/PSE cold suspension 10 mL 110 mg/15 mg/5 mL PSE 10 mL 15 mg/5 mL IBU 10 mL 100 mg/5 mL IBU/PSE 5 mL 110 mg/15 mg/5 mL (<i>N</i> = 9) PSE 5 mL 15 mg/5 mL (<i>N</i> = 10)	No PK interaction between ibuprofen and pseudoephedrine PK profile of pseudoephedrine in combination suspension similar to that in single ingredient suspension in pediatrics 2–5 years of age	PK and safety data support the age/body weight based dosing
	PK; single-dose, randomized, open label, parallel group	<i>N</i> = 19; 2–5 years	One teaspoon of IBU/PSE 110 mg/15 mg/5 mL (24–47 lb) every 6 h for 7 days (cold) or 3 days (fever) Two teaspoons of IBU/PSE 110 mg/15 mg/5 mL (48–95 lb) every 6 h for 7 days (cold) or 3 days (fever)	No serious AEs. One subject discontinued from the study due to AEs	
	Safety; multiple-dose, open label, multicenter	<i>N</i> = 106; 2–11 years			

Continued

Table 2. Continued

Drug/Reference	Study Objectives and Design	No. Subjects; Age Range	Treatments	Key Results and Conclusions	Comments
Ibuprofen/pseudoephedrine, Children's Motrin Cold NDA review package 2000 ^{39,68}	PK; multiple-dose, open label	N = 24; 4–11 years	IBU/PSE suspension ibuprofen 7.5 mg/kg/pseudoephedrine 1.125 mg/kg every 6 h for 5 days	No apparent differences in PK parameters of ibuprofen/pseudoephedrine combination and individual products, and pediatric have 50% higher clearance than adults for both ibuprofen and pseudoephedrine	PK and safety data support age/body weight based dosing regimen for children
	Safety; open label, multiple-dose	N = 124; 2–11 years	IBU/PSE suspension ibuprofen 7.5 mg/kg/pseudoephedrine 1.125 mg/kg every 6 h for 3 days	Well tolerated, no deaths, no serious AEs	
Ibuprofen/chlorpheniramine/pseudoephedrine, Children's Advil Allergy Sinus NDA review package 2004 ⁴⁰	PK; single-dose, open label, one treatment, one period	N = 28; 6–11 years	IBU/PSE/CPM 10 mL of 100 mg/15 mg/1 mg/5 mL	Systemic exposure was comparable in children and adults	PK data support the dosing regimen for children

Abbreviations: NA: not available; AR: allergic rhinitis; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; iTNSS: instant total nasal symptom score; rTNSS: reflective total nasal symptom score; AE: adverse event; PMR: Postmarketing Study Requirement; PK: pharmacokinetics; PD: pharmacodynamics; AQ: aqueous; QD: once daily; BID: twice daily; IBU: ibuprofen; PSE: pseudoephedrine; CPM: chlorpheniramine

conditions, the pediatric effectiveness was extrapolated from adequate and well-controlled efficacy studies in adults.^{47,49}

For the dosing regimen of 2.5 mg once daily for children 6–11 years of age, 1.25 mg once daily for children 12 months to 5 years of age, and 1 mg once daily for infants 6–11 months of age, the safety was also established in the three clinical safety studies conducted in pediatric patients at age 6–11 years (*n* = 120), 2–5 years (*n* = 111), 12–23 months (*n* = 65), and 6–11 months (*n* = 66) at dose 2.5, 1.25, 1.25, and 1 mg, once daily, respectively.^{20,47,49} These studies were all 15-day treatment, randomized, double-blind, placebo-controlled, parallel-group safety studies. The results of these studies showed that desloratadine was well tolerated, and no serious adverse events (AEs) were reported in pediatric subjects 6 months to 11 years at the proposed doses.^{47,49} The safety measures in pediatric poor metabolizers receiving desloratadine were similar to those in pediatric normal metabolizers with or without desloratadine.

Fexofenadine

The proposed dose for fexofenadine hydrochloride in pediatric SAR patients 2 to 11 years of age is based on PK and safety data, formulation bridging, efficacy extrapolation from adults, and efficacy assessment in SAR patients 6–11 years of age. The PK exposure of pediatric patients aged 6–11 years given 30 mg dose was comparable to that of adults given a 60 mg dose. Population modeling and simulation showed that the apparent oral clearance estimate of fexofenadine was 44% lower in pediatric subjects aged 6–12 years, compared to adult subjects. Efficacy and safety of fexofenadine at doses of 15, 30, and 60 mg (tablet) twice daily were evaluated in two 2-week, multicenter, randomized, placebo-controlled, double-blind trials in 877 SAR patients 6–11 years of age (60 mg twice daily was considered an appropriate dose for adults).²¹ All three doses significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) as compared to placebo. However, dose response relationship was not apparent and the 60 mg twice daily did not provide any additional benefit over the 30 mg dose twice daily.^{21,51} Fexofenadine 30 mg given twice daily is thus recommended for children 6–11 years of age.²¹

For children 2 to 6 years of age, PK and safety were evaluated.⁵⁰ Fexofenadine was well tolerated, and no unexpected AEs were observed. Population analysis showed that the apparent oral clearance estimate of fexofenadine was 36% lower in pediatric subjects 2 to 5 years compared to adult subjects.^{21,71} As the clinical formulation in the PK and safety studies were not suited for marketing, an oral suspension formulation was developed later as the to-be-marketed formulation. The formulation bridging program comprised of three PK studies to evaluate the bioavailability, bioequivalence and food effect of the suspension formulation. Administration of fexofenadine suspension of 30 mg to children 2 to 6 years of age resulted in exposure comparable to those in adults given 60 mg dose and children 6 to 12 years of age given 30 mg dose. The bioequivalence was established between the fexofenadine suspension and the reference product. Administration with food decreased the rate and extent of exposure of fexofenadine. Based on PK, safety of fexofenadine and an efficacy extrapolation from adults, 30 mg twice daily was proposed for children 2–5 years of age and the food effect is noted in the label.⁵⁰

Levocetirizine

The proposed dose of levocetirizine dihydrochloride in pediatric AR patients 6 months to 11 years of age is based on the PK and safety data, formulation bridging and efficacy extrapolation from adult subjects. Levocetirizine is formulated as 5 mg tablets and 2.5 mg/5 mL (0.5 mg/mL) oral solution. Bioequivalence between these two formulations was demonstrated in the healthy adult population.⁷² The efficacy in pediatric patients younger than 12 years of age was extrapolated from adult efficacy trials based on PK comparison. In a study conducted in 14 pediatric AR patients of 6–11 years with body weight between 20 and 40 kg and a single dose of 5 mg tablet, the systemic exposure was twice that of healthy adults given the same dose.^{52–54} The safety of levocetirizine in AR patients 6 to 12 years of age was evaluated in two clinical trials and the 5 mg once daily dose for 4 to 6 weeks was safe and well tolerated. Therefore, 2.5 mg once daily was recommended in children 6–11 years of age.

The clinical program consisted of two safety trials in children from 6 months to <6 years of age with SAR, PAR, or chronic idiopathic urticaria. The two safety studies were 2-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies.⁵⁴ A total of 69 patients 6–11 months of age were randomly administered 1.25 mg once daily or placebo, and a total of 173 patients 1–5 years of age were randomly given 1.25 mg twice daily or placebo. These two studies demonstrated that AEs (e.g., somnolence and excitability) were similar to those in the placebo group. No dedicated PK studies were conducted in pediatric patients younger than 6 years of age. A population PK modeling and simulation analysis showed that exposure in children 6 months to 5 years of age given 1.25 mg once daily were comparable to that adults given 5 mg once daily. Therefore, a 1.25-mg once daily dosing was proposed for the pediatric patients 6 months to 5 years of age.

Loratadine

One PK study and one safety study were reported in patients 2–5 years of age. The PK study was a single-dose, open-label study in 18 subjects. The variability and range of exposure of loratadine 5 mg syrup were comparable to that for a 10 mg tablet or syrup in healthy adult subjects or children 8 years of age and older.⁵⁶ The safety of loratadine 5 mg syrup once daily was evaluated in a randomized, placebo-controlled, parallel group 2-week study in 121 patients 2–5 years of age.⁵⁷ No deaths or serious events occurred in the trials, and no patients discontinued due to any AEs. Therefore, 5 mg dose once daily was selected for the pediatric patients 2–5 years of age. The PK and safety were also assessed in children 6 to 12 years of age. As seen in younger children, the range and variability of PK exposure loratadine in children in the 6–12 years of age was similar to that of adults.²⁴ The safety of loratadine syrup at 10 mg once daily in children 6 to 12 years of age was demonstrated in a placebo-controlled, double-blind, 2-week trial in 188 pediatric patients with SAR. Therefore, 10 mg dose once daily was proposed for the pediatric patients 6–11 years of age. The efficacy of loratadine syrup for the treatment of seasonal AR in children 2–12 years of age was based on an extrapolation of the efficacy of loratadine in adults because of the likelihood that the disease course, pathophysiology, and the drug's effect are similar to that of the adults.²⁴

Cetirizine

The PK and safety of cetirizine in children 6 months to <2 years of age were evaluated, and systemic exposure given maximum dose of cetirizine solution (2.5 mg twice daily) was expected to be two-fold higher than that observed in adults given 10 mg cetirizine tablets once daily. The safety of proposed doses in different age group (5 or 10 mg/day for 6–11 years of age, 0.2–0.4 mg/kg twice daily for 2–5 years of age, 0.25 mg/kg twice daily for 12–24 months of age) was assessed in different safety studies, and results demonstrated that all the doses were well tolerated and no unexpected safety findings were reported.⁴⁴ PK modeling and simulation indicated that PK exposure of cetirizine at 2.5 mg dose (2–5 years of age) and 5 mg dose (6–11 years of age) was estimated to be similar to adults given 10 mg.⁵⁹ The efficacy of cetirizine for the treatment of AR in pediatric patients is based on an extrapolation of the demonstrated efficacy of cetirizine in adults with these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are similar between these two populations.⁵⁹ Therefore, 2.5 mg once daily and 5 mg once daily are proposed for children 6 months to 5 years and children 6 to 11 years, respectively.

Intranasal Antihistamine

Olopatadine

Olopatadine nasal spray, an H₁ receptor antagonist, is indicated for the relief of the symptoms of seasonal AR in adults and children 6 years of age and older. Each 100 µL spray contains 665 µg of olopatadine hydrochloride. The proposed dose for olopatadine nasal spray in pediatric patients 6 to 11 years of age is mainly based on efficacy and safety data, whereas PK assessment is useful for systemic exposure.

Three clinical trials were conducted to evaluate the PK, safety, and efficacy of olopatadine in SAR patients.⁵⁸ The PK assessment was conducted after multiple dose administration in pediatric patients aged 6–11 years. Olopatadine 0.6% nasal spray were given to 42 patients twice daily for 14.5 days. The mean C_{max} of olopatadine following olopatadine nasal spray 0.6% one spray per nostril twice daily in patients 6–11 years of age was about 2-fold less than that in adults and adolescent 12 years of age and older with two sprays per nostril twice daily while mean AUC was comparable to that in adults and adolescents. These differences are not considered clinically significant.

Each of the two efficacy and safety studies was a 2-week, double-blind, parallel group, vehicle-controlled trial in SAR patients 6–11 years of age.⁵⁸ One study used the dose of olopatadine 0.6% nasal spray and vehicle control twice daily for 2 weeks, whereas the other study used the dose of olopatadine at two concentrations (0.4% and 0.6%) nasal spray, one spray per nostril twice daily for 2 weeks. The primary efficacy endpoint was the difference from placebo in the percentage change from baseline in the average morning and evening reflective total nasal symptom score (rTNSS) averaged for the 2-week treatment period. Patients in the study with olopatadine 0.6% Nasal Spray, one or two sprays per nostril twice daily, had statistically significant greater decreases in rTNSS compared to vehicle nasal spray whereas the study with olopatadine at two concentrations was not successful. The safety was also demonstrated in olopatadine nasal spray given one or two

sprays per nostril twice daily in the study. As a result, one spray per nostril twice daily was proposed in children 6–11 years of age.⁵⁸

LEUKOTRIENE RECEPTOR ANTAGONIST

Montelukast

Montelukast is a leukotriene receptor antagonist that binds to the cysteinyl leukotriene receptor 1 with high affinity and selectivity.²³ There was no clinical efficacy trial conducted in pediatric SAR or PAR patients. The dose selection for pediatric AR patients was based on PK and safety data and efficacy extrapolation from adult patients. The systemic exposure of montelukast given as one 4 mg chewable tablet to pediatric patients 2–5 years of age and one 5 mg chewable tablet to pediatric patients 6–14 years of age was similar to that given as one 10 mg film-coated tablet in adults. Population PK modeling and simulation showed that there was no correlation between clearance, volume distribution, and weight or age in pediatrics 6 months to <2 years of age, suggesting the fixed dose approach is appropriate in this age group. The efficacy of montelukast for the SAR in pediatric patients 2–14 years of age and for PAR in pediatric patients 6 months to 14 years of age was supported by extrapolation from the efficacy in patients 15 years of age and older with SAR and PAR assuming that the disease course, pathophysiology and the drug effect are similar among these populations. The safety profiles of montelukast in the patients 2–14 years of age were similar to the placebo group in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group study.²³ This information was also applied to the PAR population at the same age group. The safety in patients 6–23 months of age is supported with the safety data in pediatric asthma patients and PK data in the same age group.

INTRANASAL CORTICOSTEROID

Intranasal corticosteroid are considered effective and safe first-line treatment for AR; however, the safety of these compounds remains a topic of discussion.⁷³ The intranasal corticosteroids can be absorbed through airway and gastrointestinal routes; most of the dose being swallowed.⁷⁴ The current approved intranasal corticosteroids in the treatment of pediatric AR, such as mometasone, triamcinolone, and ciclesonide, are mainly metabolized in the liver and have a very low oral bioavailability; however, there is considerable variability in bioavailability of the intranasal corticosteroids.⁷⁵ Clinical studies have shown that the corticosteroids may have potential effect on hypothalamic–pituitary–adrenal (HPA) axis suppression particularly in pediatric population who may be a more vulnerable population.⁷⁶ Therefore, HPA axis assessments are recommended in the clinical program for the intranasal corticosteroids.

Triamcinolone

Triamcinolone nasal spray is a corticosteroid indicated for the treatment of nasal symptoms of SAR and PAR in adults and children 2 years of age and older. Triamcinolone dose in pediatric AR patients 2 years of age and older was selected based on efficacy and safety data. Plasma concentrations were also monitored to evaluate systemic exposure. The safety and efficacy of triamcinolone at doses of 110 or 220 µg once daily were

studied in two double-blind, placebo-controlled studies of 2- and 12-week duration in 518 SAR and PAR patients 6–12 years of age.²⁷ The results indicated that both doses significantly reduced the severity of nasal symptoms of AR compared with placebo arm. Banov et al. also reported that 220 µg once daily for 2 weeks was effective and safe in 116 SAR patients 6–11 years of age.⁷⁷ The safety of 220 µg once daily was also evaluated with adrenal function tests for 6 weeks in children 6–12 years of age.⁶² No abnormal response to cosyntropin infusion (peak serum cortisol <18 µg/dL) was observed.⁶² Therefore, 110 µg/day was proposed as the starting dose and 220 µg/day was proposed as the maximum dose for children 6–11 years of age.

PK exposure of triamcinolone in pediatric patients of 2–5 years of age given 110 µg once daily was similar to that in adults receiving dose 220 µg once daily. Population pharmacokinetic modeling and simulation indicated that the apparent clearance and volume of distribution of triamcinolone in pediatric patients 2–5 years of age were approximately half of those in adults.²⁷ The 110 µg dose was evaluated in a randomized, double-blind, placebo-controlled study. A total of 464 PAR patients were randomly given triamcinolone 110 µg or placebo once daily in the morning. The 110 mcg once daily provided statistically significantly greater improvement from baseline for 24-hour rTNSS over the 4 week treatment period as compared to placebo ($p = 0.033$). The safety data from this study showed that the AEs were consistent with AEs typically noted in clinical trials with SAR and PAR. The results for the HPA axis assessment in children 2–5 years of age is inconclusive, suggesting that a subset of patients might be more susceptible to the effects of corticosteroids. The 110 µg once daily was proposed for the 2–5 years of age group, however, subjects sensitive to the effects of corticosteroids should be cautioned.

Ciclesonide

Ciclesonide nasal spray is a corticosteroid indicated for relieving nasal symptoms associated with SAR in adults and children 6 years of age and older and PAR in adults and adolescents 12 years of age and older.²⁸ The selected dose for ciclesonide in pediatric AR patients was based on efficacy and safety data. Plasma concentrations were only sporadically measurable at investigated doses due to low systemic exposure.

The efficacy and safety of ciclesonide nasal spray were evaluated in two randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of 2 and 12 weeks in duration in pediatric patients.⁶³ In one trial, ciclesonide nasal spray was administered at 200 and 100 µg once daily for 2 weeks in SAR patients 6 to <12 years of age. In the other trial, ciclesonide nasal spray of 200 µg of once daily for 12 weeks was administered in PAR patients 2 to <6 years of age. The primary efficacy endpoint was the difference from placebo in the change from baseline of the average of morning (AM) and evening (PM) rTNSS averaged over 2 weeks of treatment in the SAR trial. The primary objective of the 12-week trial was safety. However, efficacy was also assessed in the PAR patients of 2 to <6 years of age. In the 2 weeks SAR trial, the mean AM and PM rTNSS and AM iTNSS 200 µg once daily dose (not 100 µg daily dose) were statistically significantly different from placebo. In the 12-week trial in patients with PAR 2 to <6 years of age, efficacy was not established. Therefore, the dose was proposed at 200 µg down to 6 years of age in SAR patients only.⁶³

The adrenal function in patients 2–11 years of age with PAR at daily doses of 200, 100, and 25 µg was evaluated in a 12-week study (6–11 years of age) and a 6-week study (2–5 years of age), respectively.^{28,78} The results indicated that ciclesonide-treated groups had a numerically greater decline in 24-h urinary free cortisol compared to the placebo-treated group. Therefore, subjects sensitive to the effects of corticosteroids should be cautioned.

Mometasone

Mometasone furoate nasal spray is indicated for the treatment of nasal symptoms associated with AR in patients ≥ 2 years of age.²⁹ Use of mometasone furoate nasal spray 50 µg for AR in pediatric patients 2–11 years of age is supported by safety and efficacy data from clinical studies. The efficacy and safety were demonstrated in four clinical trials, and a total of 990 SAR or PAR patients 3–11 years of age were given mometasone nasal spray.^{64,65} Meltzer et al.⁶⁴ conducted a dose-ranging study in children 6–11 years of age with SAR in a 4-week, multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group study. The patients were randomized to one of five treatment arms: 25 µg mometasone nasal spray daily ($n = 137$), 100 µg mometasone nasal spray daily ($n = 135$), 200 µg mometasone nasal spray daily ($n = 133$), 84 µg beclomethasone dipropionate (BDP) twice daily ($n = 138$), and placebo ($n = 136$). All doses of mometasone and BDP were significantly more effective in reducing total nasal symptom scores than was placebo ($p < 0.02$). Mometasone 25 µg daily was significantly less effective than were the other active treatments ($p < 0.05$). No additional benefit was observed for the 200 µg mometasone furoate total daily dose compared with 100 µg mometasone furoate total daily dose in pediatric patients. Twenty-eight patients 2–5 years of age with AR were treated with mometasone nasal spray 50 µg (100 µg total daily doses) in a controlled trial to evaluate safety. Therefore, one spray (50 µg in each spray) per nostril once daily (100 µg total daily dose) was proposed for the pediatric patients 2–11 years of age.²⁹

The effect of mometasone furoate nasal spray on adrenal function was assessed in three clinical studies at daily dose up to 200 µg versus placebo in AR patients 6–11 years of age ($n = 48$), 3–5 years of age ($n = 48$), and 2–5 years of age ($n = 52$). No statistically significant decrease in mean plasma cortisol levels nor 24-h urinary free cortisol levels were seen compared to placebo.

IBUPROFEN AND ITS COMBINATION THERAPY

As ibuprofen is often used in combination products for cough and cold, literature summary is presented here. Ibuprofen is a propionic acid derivative of the nonsteroidal anti-inflammatory class of drugs. It has a long history of use, first as a prescription medication since 1969 and subsequently as an OTC product for adults and children over 12 years of age since 1984, and for children between 2 and 12 years of age since 1995. It is currently available in four different formulations for the pediatric populations: oral drops, suspension, chewable tablets, and tablets, all of which have been approved for OTC use for temporary relief of minor aches and pains and reduction of fever in children. On April 15, 1999, the OTC use of ibuprofen was extended from 2 years to 6 month of age.⁷⁹

Ibuprofen Monotherapy

The safety profile of ibuprofen has been widely evaluated in traditional pediatric clinical trials of fever and/or pain or in critical reviews.^{80,81} All have shown the low incidence of AEs with ibuprofen. Lesko and Mitchell have published several papers comparing the safety of ibuprofen and paracetamol with a focus particularly on ibuprofen.^{82–84} In a randomized, double-blind, paracetamol (acetaminophen)-controlled trial, a total of 84,192 patients 6 months to 12 years of age were randomly assigned to receive ibuprofen 5 mg/kg ($n = 27,948$) or ibuprofen 10 mg/kg suspensions ($n = 27,837$), or 12 mg/kg paracetamol suspension ($n = 28,130$) for the treatment of acute fever for 4 weeks.⁸² This study showed that the short-term risk for hospitalization due to gastrointestinal bleeding, acute renal failure, anaphylaxis, and Reye's syndrome associated with the use of high and low dose ibuprofen in this trial was not different from the risk in children treated with acetaminophen. Another large investigation was known as the Children's Analgesic Medicines Project.⁸⁵ The objective of the study was to evaluate the actual clinical experience with ibuprofen as compared to acetaminophen. It was a prospective, multicenter, multiple-dose, randomized, and open label study. It compared the safety of ibuprofen with that of paracetamol given for relief of pain and/or fever. A total of 41,810 children aged 1–18 years, including 14,291 children < 2 years of age, were enrolled in 68 clinics in the United States. There were no cases of anaphylaxis, gastrointestinal bleeding, renal failure, Reye syndrome reported in children < 2 years of age, and there were no serious AEs in $\geq 1\%$ of patients in either group.

The combination products containing ibuprofen for the pediatric cough and cold patients include ibuprofen/pseudoephedrine/chlorpheniramine and ibuprofen/pseudoephedrine. Same as ibuprofen, pseudoephedrine and chlorpheniramine are each approved and sold OTC as single ingredients or in combination for children and adults as well.

Ibuprofen/Pseudoephedrine/Chlorpheniramine

The triple combination of ibuprofen, pseudoephedrine, and chlorpheniramine is approved as a tablet formulation for children 12 years of age and older and as suspension formulation for children 6 to 11 years old. Use of the triple combination of ibuprofen, pseudoephedrine, and chlorpheniramine as suspension formulation for children 6 to 11 years old is supported by PK and safety data, formulation bridging, and efficacy extrapolation from adult triple combination tablet program. The PK and safety studies included two single dose PK studies and one multiple dose safety study in children 6–11 years of age.⁴⁰ The first study was a three-way crossover bioavailability/food effect study in healthy adults. The results show that exposures of individual component in the suspension formulation were comparable to those of the reference formulation and the presence of food did not result in a clinically relevant change in the rate and extent of absorption of ibuprofen, pseudoephedrine, and chlorpheniramine from the combination suspension. The second study was a one-period, one-treatment, open-label, single-dose PK study (10 mL dose of suspension) in children 6–11 years of age with symptoms of AR ($n = 28$). The systemic exposure data demonstrated that the rate and extent of absorption of ibuprofen, pseudoephedrine, and chlorpheniramine in the combination suspension were similar between children (between

6 and <12 years of age) and adolescents and adults (>12 years of age). These two PK studies support the efficacy extrapolation from adult efficacy data from the approved triple combination tablet containing ibuprofen 200 mg/pseudoephedrine 30 mg/chlorpheniramine 2 mg.

The safety data were derived from a pivotal safety study, two PK studies, postmarketing surveillance data, the literature, reports from the American Association of Poison Control Centers, reports from the Drug Abuse Warning Network, Emergency Department reports, and 4-month safety update. All the safety databases support the safety of the triple combination suspension in children at the proposed doses. No safety concerns beyond what is already known about each of the active ingredient in the product were noted.⁴⁰

Ibuprofen/Pseudoephedrine

Use of combination product of ibuprofen 100 mg and pseudoephedrine 15 mg in 5 mL suspension formulation in children 2 to 11 years old is supported by PK and safety data. PK and safety were assessed in two PK and one safety studies.^{66,67} PK studies included one single dose, randomized, open-label, single center, three-way crossover study in 28 healthy children 6–11 years of age given 10 mL ibuprofen 110 mg/pseudoephedrine 15 mg/5 mL, 10 mL pseudoephedrine 15 mg/5 mL, and 10 mL ibuprofen 100 mg/5 mL; and one single dose, randomized, open label, multicenter, parallel group study in 19 patients 2–5 years of age with an acute upper respiratory tract infection given 5 mL ibuprofen 110 mg/pseudoephedrine 15 mg/5 mL, or 5 mL pseudoephedrine 15 mg/5 mL. The results demonstrated that the rate and extent of absorption of ibuprofen and pseudoephedrine in combination were similar to those of the individual components and similar across the age groups. The data also suggested that the younger age group had a higher clearance (after body weight normalization) for both ibuprofen and pseudoephedrine.^{66,67} The safety was assessed in an open-label, multiple-dose, single treatment, multicenter study of ibuprofen 110 mg/pseudoephedrine 15 mg/5 mL in children 2–11 years of age. The dose used was one teaspoon (5 mL) for subjects weighing 24–47 lb and two teaspoons (10 mL) for subjects weighing 48–95 lb. The subjects received the same dose every 6 h up to four times daily, and for no more than 7 days for the symptoms of cold or for no more than 3 days for fever. A total 28% of subjects reported AEs, which was considered typical of clinical trials with similar treatments. There were no unexpected AEs beyond what are already known about the two active ingredients in the product.^{66,67} The safety study and literature review were supportive of safety of the combination product of ibuprofen and pseudoephedrine. Therefore, the the investigated two-tiered pediatric dosing based on age and body weight was proposed in pediatric patients 2 to 12 years of age.³⁶

Another combination product of ibuprofen 100 mg/5 mL and pseudoephedrine HCl 15 mg/5 mL is also marketed OTC with the same dosing regimen in children 2–11 years of age.

The PK and safety of ibuprofen/pseudoephedrine suspension were evaluated in one multiple dose PK study in 24 healthy pediatrics 4–11 years of age given ibuprofen 7.5 mg/kg/pseudoephedrine 1.125 mg/kg every 6 h for 5 days; and one 3-day multiple dose safety study in 124 patients with cold 2–11 years of age given same dose and dose interval for 3 days.⁶⁸ The results indicated that PK parameters for the ibuprofen/

pseudoephedrine combination product were comparable to the individual active ingredients in children down to 4 years of age. The pediatric population had a 50% increased clearance for both ibuprofen and pseudoephedrine compared to adults. No serious AEs were seen in these studies. Safety data from these pediatric studies, the ibuprofen/pseudoephedrine combination in adults and the individual products support the use of the combination in pediatric patients to 2 years of age. One single dose, crossover bioequivalence study in 24 healthy adults demonstrated no interaction between ibuprofen and pseudoephedrine. Although the body-weight based dosing regimen used in the PK and safety studies was safe and well tolerated, the two-tiered dosing regimen based on weight and age was suggested in the pediatric patients 2 to 11 years of age so that the maximum daily dose of pseudoephedrine was within the range of monograph recommendation.⁶⁸

SUMMARY

This review summarizes the pediatric drug development for 14 drugs used in the treatment of AR, cough, and cold. The use of these drugs in pediatric patients is based upon the assessment of PK, safety, and efficacy data. As the disease course, pathophysiology and the drug's effect are considered similar in young pediatrics to that of adult patients for AR, cough, and cold, the efficacy of orally administered drugs in pediatric patients are generally extrapolated from adults or older pediatrics. For some oral antihistamines, such as fexofenadine, the proposed dose in pediatric SAR patients 2 to 11 years of age is based on PK and safety data, efficacy extrapolation from adults as well as the efficacy assessment in SAR patients 6–11 years of age. For other oral antihistamine drugs and leukotriene modifier, such as desloratadine, levocetirizine, loratadine, cetirizine, and montelukast, the selected dose in pediatric patients is based on PK and safety data in pediatric patients and efficacy extrapolation from adults to pediatric patients. Age appropriate formulations were developed for pediatric population for most oral antihistamine drugs and a bioequivalence study conducted in adults demonstrated equivalence between the pediatric formulation and adult formulation. Additional biopharmaceutical studies have also been conducted to assess bioavailability and food effect for the pediatric formulations in certain cases. For locally acting drugs, such as intranasal antihistamine (e.g., olopatadine) and intranasal corticosteroids (e.g., triamcinolone), as systemic exposure is not consistently detectable or reliable as measures of local bioavailability and efficacy, the proposed dose regimen was based mainly on the clinical efficacy and safety data. Plasma concentrations were also monitored, if measurable, to evaluate systemic exposure.

Ibuprofen has been on market well over 50 years, and the approval for pediatric use was based largely on PK and safety data in pediatric patients. For the combination products of ibuprofen with other monograph drugs like pseudoephedrine and/or chlorpheniramine, the dose selection in pediatric patients is based on PK and safety data and efficacy extrapolation from adults. The maximum daily dose should be within the monograph recommended maximum daily dose.

In conclusion, for the AR, cough, and cold drugs, pediatric dosing is determined by the totality of evidence. Assessment includes factors such as PK, safety, efficacy, and formulation, each of which plays a role in supporting the approval of drugs

for pediatric populations. The knowledge and understanding of information summarized in this review will help the future trial design and regulatory decision making for new drugs or combination products in AR, cough, and cold indication or other disease areas for the pediatric drug development.

REFERENCES

1. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, Li JT, Bernstein IL, Berger W, Spector S, Schuller D. 1998. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 81:478–518.
2. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H. 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 368:733–743.
3. Togias A. 2001. Systemic cross-talk between the lung and the nose. *Am J Respir Crit Care Med* 164:726–727.
4. Millqvist E, Bende M. 2006. Role of the upper airways in patients with chronic cough. *Curr Opin Allergy Clin Immunol* 6:7–11.
5. Chang AB, Harghy VA, Simpson J, Masters IB, Gibson PG. 2002. Cough, airway inflammation, and mild asthma exacerbation. *Arch Dis Child* 86:270–275.
6. Consumer Healthcare Products Association. 2007. Key findings of a national survey on cough medicine use. Accessed July 5, 2013, at: <http://www.chpa-info.org/media/resources/r.4510.pdf>.
7. U.S. Food and Drug Administration. 2012. Public health advisory: FDA recommends that over-the-counter (OTC) cough and cold products not be used for infants and children under 2 years of age. Accessed July 6, 2013, at: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforhealthcareprofessionals/publichealthadvisories/ucm051137.htm>.
8. U.S. Food and Drug Administration. 2008. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children. Accessed July 6, 2013, at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm>.
9. U.S. Food and Drug Administration. 2002. Best Pharmaceuticals for Children Act 2002. Public Law 107-109. Accessed July 6, 2013, at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107_cong_public_laws&docid=f:publ109.pdf.
10. U.S. Food and Drug Administration. 1997. Food and Drug Administration Modernization Act of 1997. Accessed July 6, 2013, at: <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendments/totheFDCA/FDAMA/FullTextofFDAMALaw/UCM089145.pdf>.
11. U.S. Food and Drug Administration. 2003. Pediatric Research Equity Act of 2003. Accessed July 6, 2013, at: <http://www.gpo.gov/fdsys/pkg/PLAW-108publ155/html/PLAW-108publ155.htm>.
12. U.S. Food and Drug Administration. 1998. The Pediatric Rule. 63 FR 66632, December 2, 1998. Accessed July 6, 2013, at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3927B1_05_1998%20Pediatric%20Rule.pdf.
13. Skoner DP. 2001. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 108:S2–S8.
14. Blaiss MS. 2004. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin* 20:1937–1952.
15. Scadding G. 2008. Optimal management of nasal congestion caused by allergic rhinitis in children: safety and efficacy of medical treatments. *Paediatr Drugs* 10:151–162.
16. Cox L, Calderon M, Pfaar O. 2012. Subcutaneous allergen immunotherapy for allergic disease: Examining efficacy, safety and cost-effectiveness of current and novel formulations. *Immunotherapy* 4:601–616.
17. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. 2007. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* CD001936.
18. Albert AM, Li M, Victor VJ, Abdullah J, Chui CS, Tsen S, Chun CT, Au T, Hugh HS, Lam S, Hung HK, So K, Michael MH, Chan HM, Alex AW, Leung WK, Iris IH, Chan HS, Christopher CW, Lam WK, Pak PC, Ng C. 2009. Leukotriene receptor antagonist in the treatment of childhood allergic rhinitis—a randomized placebo-controlled study. *Pediatr pulmonol* 44: 1085–1092.
19. U.S. Food and Drug Administration. 2012. Advisory Committee for pharmaceutical science and clinical pharmacology meeting briefing information. Accessed July 6, 2013, at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM295209.pdf>.
20. U.S. Food and Drug Administration. 2004. Clarinex label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/213001bl.pdf.
21. U.S. Food and Drug Administration. 2008. Allegra label. Accessed July 2, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020872s018,021963s002bl.pdf.
22. U.S. Food and Drug Administration. 2006. Clinical pharmacology review for NDA 21963. Accessed July 2, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021963s000.ClinPharmR.pdf.
23. U.S. Food and Drug Administration. 2012. Singulair label. Accessed July 6, 2012, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021409s036l.pdf.
24. U.S. Food and Drug Administration. 2000. Claritin label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20641s7l.pdf.
25. U.S. Food and Drug Administration. 2004. Zyrtec label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/19835slr016,21150slr005,30346slr011.zyrtec.l.pdf.
26. U.S. Food and Drug Administration. 2010. Patanase label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021861s008l.pdf.
27. U.S. Food and Drug Administration. 2008. Nasacort AQ label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020468s024l.pdf.
28. U.S. Food and Drug Administration. 2010. Omnisar label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022004s005l.pdf.
29. U.S. Food and Drug Administration. 2011. Nasonex label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020762s044l.pdf.
30. U.S. Food and Drug Administration. 1998. Children's Advil label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20944.Advil.prntl.pdf.
31. U.S. Food and Drug Administration. 2011. Advil label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018989Orig1s079l.pdf.
32. U.S. Food and Drug Administration. 2000. Pediatric Advil label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/020812s003l.pdf.
33. U.S. Food and Drug Administration. 1999. Children's Motrin label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20-603S002.Ibuprofen.prntl.pdf.
34. U.S. Food and Drug Administration. 2010. Motrin IB label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019012s046l.pdf.
35. U.S. Food and Drug Administration. 2002. Infants' Motrin label. Accessed July 6, 2012 at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20603s5l.pdf.

36. U.S. Food and Drug Administration. 2002. Children's Advil Cold label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/213731bl.pdf.
37. U.S. Food and Drug Administration. 2003. Advil Cold & Sinus label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21374SLR001_Advil_lbl.pdf.
38. U.S. Food and Drug Administration. 2001. Advil Cold and Sinus label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/19771S20lbl.pdf.
39. U.S. Food and Drug Administration. 2000. Clinical pharmacology review for NDA 21128. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-128.CHILDREN'S%20MOTRIN%20COLD%20SUSPENSION.BIOPHARMR.PDF.
40. U.S. Food and Drug Administration. 2004. Medical review for NDA 21587. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-587_Advil_medr.pdf.
41. U.S. Food and Drug Administration. 2004. Advil Allergy Sinus label. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21441slr001_advil_lbl.pdf.
42. Novak E, Allen PJ. 2007. Prescribing medications in pediatrics: concerns regarding FDA approval and pharmacokinetics. *Pediatr Nurs* 33:64–70.
43. Johnson TN, Tucker GT, Rostami-Hodjegan A. 2008. Development of CYP2D6 and CYP3A4 in the first year of life. *Clin Pharmacol Ther* 83:670–671.
44. U.S. Food and Drug Administration. 2002. Review package for NDA 20346/S008. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/020346.S008.ZYRTEC%20TABLETS.pdf.
45. U.S. Food and Drug Administration. 2000. Draft guidance for industry. Allergic rhinitis: Clinical development programs for drug products. Accessed July 6, 2013, at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071293.pdf>.
46. U.S. Food and Drug Administration. 2003. Guidance for industry: Exposure-response relationship-study design, data analysis, and regulatory applications. Accessed July 6, 2013, at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.
47. U.S. Food and Drug Administration. 2004. Medical review for NDA 21300. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021300s000.Clarinex_MedR.pdf.
48. U.S. Food and Drug Administration. 2004. Clinical pharmacology review for NDA 21300. Accessed December 13, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021300s000.Clarinex_ClinPharmR.pdf.
49. U.S. Food and Drug Administration. 2004. Medical review for NDA 21563. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021563s000.Clarinex_MedR.pdf.
50. U.S. Food and Drug Administration. 2006. Medical review for NDA 21963. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021963s000.MedR.pdf.
51. U.S. Food and Drug Administration. 2000. Review package for NDA 20872. Accessed July 2, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20-872_Allegro.cfm.
52. Simons FE, Simons KJ. 2005. Levocetirizine: Pharmacokinetics and pharmacodynamics in children age 6 to 11 years. *J Allergy Clin Immunol* 116:355–361.
53. U.S. Food and Drug Administration. 2007. Clinical pharmacology review for NDA 22064. Accessed July 5, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022064s000.ClinPharmR.pdf.
54. U.S. Food and Drug Administration. 2011. Xyzal label. Accessed July 5, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022064s020,022157s007lbl.pdf.
55. U.S. Food and Drug Administration. 2009. Clinical pharmacology review for NDA 22064, S017. Accessed July 6, 2013, at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM188184.pdf>.
56. U.S. Food and Drug Administration. 2000. Clinical pharmacology review for NDA 20641 SE5-007. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20-641S007.Loratadine.biopharmr.pdf.
57. U.S. Food and Drug Administration. 2000. Medical review for NDA 20641 SE5-007. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20-641S007.Loratadine_medr.pdf.
58. U.S. Food and Drug Administration. 2009. Medical review for NDA 21861 SE5-002. Accessed July 6, 2013, at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM289256.pdf>.
59. U.S. Food and Drug Administration. 1998. Review package for NDA 19835/S005. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/19835-S005.Zyrtec.pdf.
60. U.S. Food and Drug Administration. 2008. Medical review NDA 20468-S24. Accessed July 6, 2013, at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM226045.pdf>.
61. Weinstein S, Qaqundah P, Georges G, Nayak A. 2009. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in children aged 2 to 5 years with perennial allergic rhinitis: a randomized, double-blind, placebo-controlled study with an open-label extension. *Ann Allergy Asthma Immunol* 102:339–347.
62. Nayak AS, Ellis MH, Gross GN, Mendelson LM, Schenkel EJ, Lanier BQ, Simpson B, Mullin ME, Smith JA. 1998. The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis. *J Allergy Clin Immunol* 101:157–162.
63. U.S. Food and Drug Administration. 2007. Medical review for NDA 22124. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022124s000.MedR.pdf.
64. Meltzer EO, Berger WE, Berkowitz RB, Bronsky EA, Dvorin DJ, Finn AF, Galant SP, Grossman J, Hampel FC, Ratner PH, Ruff ME, Schenkel EJ, Segal AT, Segall N, Stewart GE, Tripathy I, Skoner DP, Anolik R, Dockhorn RJ, van BJ, Mesarina-Wicki B, Nolo K. 1999. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 104:107–114.
65. Dibildox J. 2001. Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: results of recent clinical trials. *J Allergy Clin Immunol* 108:S54–S58.
66. U.S. Food and Drug Administration. 2002. Clinical pharmacology review for NDA 21373. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-373.Ibuprofen%20Pseudoephedrine.biopharmr.pdf.
67. U.S. Food and Drug Administration. 2002. Medical review for NDA 21373. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-373.Ibuprofen%20Pseudoephedrine_medr.pdf.
68. U.S. Food and Drug Administration. 2000. Medical review for NDA 21128. Accessed July 5, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-128.CHILDREN'S%20MOTRIN%20COLD%20SUSPENSION.MEDR.PDF.
69. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, Li JT, Bernstein IL, Berger W, Spector S, Schuller D. 1998. Diagnosis and management of rhinitis: Complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 81:478–518.
70. Baena-Cagnani CE. 2004. Safety and tolerability of treatments for allergic rhinitis in children. *Drug Saf* 27:883–898.
71. Krishna R, Krishnaswami S, Kittner B, Sankoh AJ, Jensen BK. 2004. The utility of mixed-effects covariate analysis in rapid selection of doses in pediatric subjects: a case study with fexofenadine hydrochloride. *Biopharm Drug Dispos* 25:373–387.
72. U.S. Food and Drug Administration. 2008. Clinical pharmacology review for NDA 22157. Accessed July 5, 2013, at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm072485.pdf>.

73. Siegel SC. 1988. Topical intranasal corticosteroid therapy in rhinitis. *J Allergy Clin Immunol* 81:984–991.
74. Allen DB. 2000. Systemic effects of intranasal steroids: An endocrinologist's perspective. *J Allergy Clin Immunol* 106:S179–S190.
75. Sizonenko PC. 2002. Effects of inhaled or nasal glucocorticosteroids on adrenal function and growth. *J Pediatr Endocrinol Metab* 15:5–26.
76. Bruni FM, De LG, Venturoli V, Boner AL. 2009. Intranasal corticosteroids and adrenal suppression. *Neuroimmunomodulation* 16:353–362.
77. Banov CH, Silvers WS, Green AW, van Bavel JH, Winder JA, Feiss G, Simpson B, Furst JA, Smith JA. 1996. Placebo-controlled, double-blind study of the efficacy and safety of triamcinolone acetonide aerosol nasal inhaler in pediatric patients with seasonal allergic rhinitis. *Clin Ther* 18:265–272.
78. U.S. Food and Drug Administration. 2007. Clinical pharmacology review for NDA 22124. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022124s000.ClinPharmR.pdf.
79. U.S. Food and Drug Administration. 1999. Review package for NDA 20603-S3. Accessed July 6, 2013, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20-603S3/InfantsMotrin.pdf.
80. Walson PD, Galletta G, Braden NJ, Alexander L. 1989. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther* 46:9–17.
81. Rainsford KD, Roberts SC, Brown S. 1997. Ibuprofen and paracetamol: relative safety in non-prescription dosages. *J Pharm Pharmacol* 49:345–376.
82. Lesko SM, Mitchell AA. 1995. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* 273:929–933.
83. Lesko SM, Mitchell AA. 1997. Renal function after short-term ibuprofen use in infants and children. *Pediatrics* 100:954–957.
84. Lesko SM, Louik C, Vezina RM, Mitchell AA. 2002. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 109:E20.
85. Ashraf E, Ford L, Geetha R, Cooper S. 1999. Safety profile of ibuprofen suspension in young children. *Inflammopharmacology* 7:219–225.