

# **FDA Briefing Document for Nonprescription Drugs Advisory Committee**

## **Triamcinolone Acetonide Nasal Spray (Nasacort AQ)**

NDA 20468

Proposed Indication:

Temporarily relieves these symptoms of hay fever or other upper  
respiratory allergies: nasal congestion, runny nose, sneezing, itchy  
nose

**Topic: Rx-to-OTC switch for triamcinolone  
acetonide nasal spray**

**Meeting Date: July 31, 2013**

## **Disclaimer Statement**

The briefing document contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the over-the-counter switch application for triamcinolone acetonide nasal spray to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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## 1. Draft Topics for Discussion

1. DISCUSSION: Please discuss the safety findings for triamcinolone acetonide nasal spray, including local nasal effects, ocular effects, immunosuppression, HPA axis effects, and growth effects for the over-the-counter (OTC) setting.
2. DISCUSSION: Discuss the proposed Drug Facts label, including statements pertaining to the risks of local nasal effects, ocular effects, immunosuppression, HPA axis effects, and growth effects.
3. VOTE: Is the risk/benefit profile of triamcinolone acetonide nasal spray supportive of OTC use for temporary relief of symptoms of hay fever or other respiratory allergies for ages 2 years and above?
  - If yes, do you have additional comments or recommendations for labeling?
  - If no, please discuss your concerns and how they can be addressed. Are there labeling changes that would address your concerns?

## **2. Summary Memorandum**

DATE: June 26, 2013

FROM: Joel Schiffenbauer, MD, Deputy Director, Division of Non-prescription Clinical Evaluation

TO: Members, NDAC and invited participants

SUBJECT: Overview of the briefing document for the Nasacort AQ (triamcinolone acetate; TAA-AQ) Nasal Spray OTC Switch

### **Introduction**

We would like to thank the committee in advance for their efforts today in regards to this meeting to discuss the switch of Nasacort AQ (triamcinolone acetonide; TAA-AQ) to the OTC market.

Nasacort AQ (triamcinolone acetonide aqueous) Nasal Spray is a suspension of the corticosteroid, triamcinolone acetonide (TAA), and is delivered as a metered dose nasal spray (55 mcg per spray). This product has been available as a treatment for seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in the United States since 1996. It is approved for use in adults and children 2 years of age and older. Currently, TAA nasal spray is available as a nonprescription product in 10 countries.

The applicant now intends to switch TAA nasal spray from a prescription to a nonprescription status for the treatment of the symptoms of hay fever or other upper respiratory allergies. This product would be a first in class to the OTC market and provides a treatment for allergic rhinitis with a mechanism of action that is different from other OTC allergy medications.

As part of this switch, the applicant has submitted a summary of efficacy and safety data from controlled clinical trials, the results of 2 post-marketing studies regarding growth effects in children and hypothalamic-pituitary axis (HPA) effects, the results of three consumer studies, as well as post-marketing safety data and an analysis of specific safety topics regarding the use of nasal steroids.

There are several products already available for use in the OTC setting for the treatment of allergic rhinitis, including oral antihistamines, oral and nasal spray decongestants, and nasal spray chromones. The use of products for this indication is familiar to the general OTC population and it is generally recognized that consumers can self-diagnose and self-select to use products for the treatment of allergic rhinitis. Use of a nasal spray formulation is also familiar to the general OTC population as nasal decongestants and nasal chromones are marketed as nasal spray products. Therefore, as part of this OTC switch program, consumer

studies examining self-selection and actual use were not requested of the applicant. However, label comprehension studies and a human factors study were performed to examine consumer understanding of the concepts regarding growth effects, preparation of the pump, and language related to safety concerns specific to the corticosteroid class.

This switch also relies on previous findings of efficacy in controlled clinical trials as well as safety from clinical trials, post-marketing reports, literature and two post marketing studies addressing growth and HPA effects. Efficacy has been established in clinical trials and, when used according to the labeled instructions, TAA nasal spray should also provide acceptable efficacy in the OTC population. Therefore, new efficacy studies were not requested and efficacy will not be a specific topic for discussion today.

The focus of this Advisory Committee (AC) will be in regards to safety topics as they relate to the use of intranasal steroids in the OTC setting and whether a consumer can use this product safely and effectively based on information provided in the drug facts label (DFL).

We look forward to your discussion.

## **General comments on OTC Considerations**

In the OTC setting, consumers must be able to understand the product label (drug facts label, DFL), self-diagnose a condition, make a self-selection decision to use the product (and select not to use a product if it is not indicated for them because, for example, they have a contraindication to use), use the product appropriately, and stop use if they get better or if they develop a serious side effect. OTC products should have a favorable safety profile such that the product can be used by a consumer without a learned intermediary.

In the case of drugs for allergic rhinitis, it is accepted that consumers can self-diagnose and self-select products that are right for them and there are already products available on the OTC market for allergic conditions. For example, oral antihistamines are indicated for treatment of symptoms of allergic rhinitis in the OTC setting and have been used appropriately and safely by consumers for years. There are also nasal sprays available OTC for the treatment of allergic rhinitis. Therefore it is reasonable to conclude that consumers should be able to self-diagnose and self-select to use TAA nasal spray based solely on information provided on the TAA nasal spray drug facts label.

Efficacy of nasal steroids has been well established based on controlled clinical trials and there is a long experience with their use in the prescription setting. There is no need to re-establish efficacy, since if used according to the labeled directions nasal steroids should provide a similar degree of symptomatic improvement whether in the prescription or OTC setting.

Furthermore, consumers should also be able to use an OTC product safely and know when to stop using it should a significant side effect develop. In the case of nasal steroids, there are a number of potential safety topics that will be discussed today. A consumer will need to be able to recognize these side effects and act accordingly, if this product is to be found acceptable for

use in the OTC market place. The committee members should keep in mind that even in the prescription setting, an individual has to be able to recognize a side effect and bring it to the attention of their physician as needed, and use in the prescription setting is contingent, at least to some extent, upon the appropriate actions of the patient. In this regard, the use by a consumer in the OTC setting is not very much different.

A challenge for us when switching a product from prescription to OTC is developing a label that addresses the important information found in the prescription label, but in consumer friendly language that captures this information and presents it within the limitations of the standard DFL (specific headings are described in our regulations, but the information included under each heading is drug specific). Prescription labels contain many, many pages of information and we are faced with determining which information is critical for the use of the product in an OTC setting.

As part of the OTC development program, we often request that sponsors conduct consumer studies which may include label comprehension, self-selection, and actual use studies. In this case, self-selection and actual use were not requested because consumers are already familiar with the concept of allergic rhinitis and can self-select to use the product correctly. However, a label comprehension study and human factors study was requested to determine if consumers could understand concepts as presented in this DFL for this product.

Therefore we would like the committee to focus the discussion on the safety topics of interest and determine, based on information provided on the drug facts label (DFL), whether all of the information necessary for the safe and effective use of the product has been successfully captured, and whether a consumer can recognize any safety concerns that may arise and act accordingly.

## **Summary of briefing package**

The briefing package contains the following information:

- 1) a summary of efficacy and safety from controlled clinical trials, including data from the growth and HPA axis studies
- 2) a summary of post-marketing safety data including specific safety issues with the use of intranasal steroids
- 3) a summary of the consumer studies
- 4) the prescription and proposed OTC labels

## **Summary of efficacy in controlled clinical trials**

We will present a very brief summary of the efficacy studies as background for a further discussion of safety. However, we intend for the AC meeting to focus the discussion on the safety profile of TAA nasal spray as presented below and how this may impact potential use in the OTC setting.

Dose selection and efficacy for the treatment of allergic rhinitis were established in the pivotal trials conducted in support of the original TAA-AQ prescription product. A total of 13 randomized, double-blind, placebo controlled trials were conducted to support the seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) indications: 10 trials in adult and adolescent patients  $\geq 12$  years of age and three pediatric trials. Efficacy was established based upon nasal symptom scores (sneezing, stuffiness, nasal discharge, and nasal itching). The results of the 13 trials were previously reviewed by the Agency and are summarized in the current approved product label. As the OTC switch application does not seek any new indications, no new clinical trial data are included in this submission.

TAA-AQ was evaluated at multiple doses in the clinical programs and determined to be effective at a dose of 220 mcg once daily in adults and adolescents 12 years of age and older. TAA-AQ was evaluated in children 6 to 12 years of age and was found to be effective for the treatment of SAR or PAR at a dose of 110 mcg once daily that can be increased to 220 mcg if necessary. TAA-AQ was evaluated at a dose of 110 mcg in children 2 to 5 years of age and was found to be effective.

## **Summary of safety**

This clinical summary of safety provides information on TAA-AQ from premarketing clinical studies, 17 years of postmarketing surveillance, and a worldwide literature search. In addition, 2 post-marketing studies examining the effects of TAA-AQ on growth and the HPA axis will be presented.

Safety has been evaluated in 43 clinical studies in which 5,558 subjects were exposed to TAA-AQ. Of these, the controlled clinical trials supporting approval evaluated a total of 1,389 adult and adolescent patients treated with TAA-AQ and a total of 575 patients 2 to 12 years of age were treated with TAA-AQ. In addition to data from the shorter efficacy and safety trials, there is pooled long-term safety data from 203 adult and adolescent patients and 578 pediatric patients 2 to 12 years of age. The potential for systemic effects with TAA-AQ has also been evaluated in specifically designed studies to address issues related to growth and HPA axis effects. These data will be discussed at the meeting.

Like all intranasal corticosteroids, prescription labeling for TAA-AQ contains Warnings and Precautions statements pertaining to the potential risks of corticosteroid use. These risks include the following:

- Local nasal effects
- Increased risk of glaucoma and/or cataracts



- Immunosuppression
- Hypercortisolism and adrenal suppression
- Reduction in growth velocity

The applicant was also requested to provide additional analyses regarding the potential effects on the sinus, and glucose and bone metabolism since these are well known class effects for corticosteroid products.

In summary, data from controlled clinical trials as well as post-marketing safety data will be presented and we will ask the committee to discuss these issues as they impact use in the OTC setting. The sponsor has included language in the proposed DFL which addresses safety information important for appropriate consumer use. We have provided a copy of the prescription as well as the OTC label and will ask the committee to assess if all of the information necessary for the safe and effective use of this product in the OTC setting as been adequately conveyed to the consumer or whether there is additional information that needs to be provided.

The next section will summarize some of the safety issues associated with the use of nasal steroids.

## **Specific safety issues**

### **Local Nasal Effects**

Intranasal corticosteroids are known to have potential local effects on the nasal cavity. Local nasal effects can range from epistaxis, localized *Candida* infections, and rarely nasal septal perforation. Epistaxis is the most commonly reported local adverse event with TAA from clinical trials, literature and postmarketing safety data sources. Nasal septal perforation was reported in a single subject in review of clinical trials/literature and based on the applicant's review was reported in a number of spontaneous cases over 16 years of marketing (see review of post-marketing cases for details).

Sinusitis with a specific etiology (i.e., bacterial, fungal infection) was rarely reported in clinical trials. In the review of clinical trials, sinusitis, without a specific etiology was reported with similar incidence rates in Nasacort AQ, active comparator and placebo groups. Review of the literature has not identified reports of infection of sinuses or nose associated with TAA treatment. The applicant performed a search of their postmarketing safety database and identified one case of fungal sinusitis, 13 cases of 'sinusitis' and one case of acute sinusitis. Additionally, 3 cases of oral fungus/oral *candida* were reported. Sinusitis is not currently listed in the prescription labeling for TAA-AQ.

The potential local effects – epistaxis, localized infections of the nose and pharynx with *Candida albicans*, and nasal septal perforation are listed in the prescription product labeling. To address this in the OTC setting, the applicant has included a warning indicating that

consumers experiencing recent nasal ulcers, surgery or trauma should not use the product until healing has occurred. The consumer is also instructed to ask a doctor before use if he has had a recent nasal ulcer, nasal surgery or nasal injury that has not healed. This language included in the proposed DFL, instructs the consumers as follows:

***Warnings***

- *Ask a doctor before use if you - have had recent nasal ulcers, nasal surgery or nasal injury that have not healed.*
- *Stop use and ask a doctor if – you have severe or frequent nosebleeds*
- *Stop use and ask a doctor if – you have or develop symptoms of an infection such as a persistent fever*
- *When using this product – do not share this bottle with anyone else as this may spread germs*

The proposed Consumer Package Insert, includes directions to:  
*Do Not Spray toward the nasal septum.*

## **Cataracts and Glaucoma**

Nasal corticosteroids may result in the development of glaucoma and/or cataracts and the prescription labeling includes a class warning. Retrospective review of clinical trial data for TAA-AQ did not reveal any adverse events of increased intraocular pressure, glaucoma, or cataracts. No reports of ocular events were identified in the literature. For details of cases from postmarketing safety surveillance regarding spontaneous reports of cataracts and intraocular pressure/glaucoma events see the medical officer review.

Language has been incorporated in the proposed DFL to address this issue. Consumers are instructed that if they have a history of, or present diagnosis of, glaucoma or cataracts to consult their physician before use and to stop product use and consult a physician if they experience any change in their vision.

The proposed DFL is included:

***Warnings***

- *Ask a doctor before use if you –have or had glaucoma or cataracts*
- *Stop use and ask a doctor if – you have any change in vision*

## **Hypercortisolism and Adrenal Suppression**

Systemic corticosteroids are known to have the potential to affect the hypothalamic pituitary adrenal (HPA) axis. While the exposure of intra-nasal corticosteroids is lower than systemic corticosteroids, Sponsors are required to assess the effect of intranasal corticosteroids on the HPA axis. The applicant has conducted four clinical studies which assess effects of TAA-AQ

on HPA axis suppression, the results of which are reflected in the current prescription label. These dedicated clinical trials in both adults and pediatric patients detected no significant differences between TAA-AQ and placebo groups.

Data from postmarketing surveillance and from the literature provide very few reports of events related to HPA axis suppression involving use of TAA-AQ and these events are often confounded by the use of other corticosteroids.

To reflect the Warning/Precaution in the prescription label regarding potential HPA axis effects, the Applicant has included language in the proposed DFL. The purpose of the language is to limit excessive use of the product.

The proposed DFL language is presented below:

***Warnings***

- *Ask a doctor before use if you – are using an asthma medicine or prescription steroid medicine*

***Directions***

- *Do not use more than directed*
- *Once allergy symptoms improve, reduce to 1 spray in each nostril per day*

## **Reduction in Growth Velocity**

Systemic corticosteroids are known to affect linear growth in children. The issue of inhaled and intranasal corticosteroids and growth in children was discussed at a Joint Pulmonary Allergy, Endocrinology and Metabolic Drugs Advisory Committee Meeting in July 1998. Based upon the discussion at the Advisory Committee meeting, the Agency required class labeling regarding the potential effects on growth for inhaled and intranasal corticosteroid products. Subsequently, a draft Guidance for Industry “Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children” published in March 2007, provided recommendations for sponsors of orally inhaled and intranasal corticosteroids regarding the design, conduct, and evaluation of clinical studies to assess the effects of these drug products on growth.

With regards to TAA-AQ, the prescription label includes the class labeling regarding the potential for growth effects. In addition the applicant has completed a postmarketing study assessing the effects of TAA-AQ on growth in pre-pubertal children. Findings from this clinical study in children aged 3 to 9 years, revealed a decrease of 0.45 cm/year in growth velocity at one year in the TAA group compared to the placebo group. This study will be presented to the AC for further discussion.

The applicant has tested the following language (see below) and has included it in the Warning section of the proposed DFL to address this issue:

*“When using this product: in children 2 to under 12 years of age:*

*-tell your child's doctor when he/she starts using this medication*  
*-this medication may temporarily slow the rate of growth in some children"*

Further in the Direction section for children 2 to under 12 years of age, the sponsor has added:  
*"When starting use, tell your child's doctor"*

## **Immunosuppression**

Use of systemic corticosteroids in general may make individuals more susceptible to infections than healthy people. This is recognized as a class effect of steroids. Corticosteroids should be used with caution, if at all, in individuals with for example, active or quiescent tuberculosis infections or untreated local or systemic fungal or bacterial infections.

While immunosuppression remains a general concern for corticosteroid use, a safety signal for immunosuppression was not identified in the clinical trial database. Rare cases have been reported in the postmarketing period, although causality could not be confirmed or excluded.

Because the prescription product labeling for intranasal corticosteroids includes a Warning regarding potential immunosuppression, the applicant has included the following language in the DFL that instructs consumers to stop use and speak to their doctor as needed:

### ***Stop use and ask a doctor if***

- *you have, or come into contact with someone who has chickenpox, measles or tuberculosis*
- *you have or develop symptoms of an infection such as a persistent fever*

In summary, the issues for the committee to address are whether consumers can recognize these effects, stop using the product if these effects develop, and seek help appropriately, based on information provided in the DFL. However, we would also be interested in knowing whether there is additional information that should be provided in the DFL to assist the consumer in dealing with these issues, should they arise.

## **Consumer study (label comprehension)**

As part of the development program for the OTC switch, two label comprehension (LC) studies and a human factors study were performed.

The applicant included language regarding the potential effects on growth velocity in children in the Warnings and Precautions Section of the prescription label for this product, similar to those for all corticosteroid products, including intranasal steroids. However, since this language is new to the OTC setting, the applicant was asked to perform a LC study to assess consumer comprehension of this information.

To develop the most appropriate language, the applicant conducted qualitative

work with consumers to help develop language for a growth statement that consumers could understand.

The following sections were added to the DFL:

- *Warnings section:*

- ***When using this product***

- ***in children 2 to under 12 years of age:***

- *tell your child's doctor when he/she starts using this medication*

- *this medication may temporarily slow the rate of growth in some children*

In the directions table, dosing instructions for children 6 to under 12 years of age and children 2 to under 6 years of age, the following was added:

- *tell your child's doctor when he/she starts using this medication*

The instruction to tell your child's doctor when he/she starts using Nasacort was understood by most subjects (96.6%, 95% CI: (93.9%, 98.3%)). The informational statement that this medication may temporarily slow the rate of growth in some children was understood by fewer of the subjects, 78.7% (95% CI: (73.7%, 83.1%)).

The proposed DFL for TAA-AQ includes several additional concepts, including language addressing local nasal effects, cataracts, and immunosuppression, which tested well for consumer comprehension.

A discussion of the consumer studies will be presented to the committee and we would like to know if the label provides adequate information for the consumer to understand the possible safety issues associated with the use of this product.

A human factors study was performed to ensure that consumers could understand how to use the pump (preparation maintenance and cleaning). This study demonstrated that the majority of participants could accurately follow the Nasacort directions for priming the bottle, re-priming the bottle and cleaning the nozzle.

## Conclusions

In the OTC setting, consumers must be able to understand the product label, self-diagnose a condition, make a self-selection decision to use (or not use) a product, and use the product correctly. OTC products should have a favorable safety profile.

During this meeting we hope to gain insights from the committee to help us decide whether the totality of the information demonstrates a favorable risk/benefit profile of TAA-AQ to support the OTC availability of this product. We will not be re-visiting the risk/benefit determination of TAA-AQ in the prescription setting, nor will we be re-visiting the appropriate use of products in general to treat allergic rhinitis in the OTC setting as this has been previously established. Efficacy has also previously been established for this product in

controlled clinical trials. The information regarding the safety profile of Nasacort is provided to inform the discussion of this proposed Rx-to-OTC switch and is the focus of this meeting.

### 3. Overview of Regulatory Background and Clinical Trials

#### Division of Pulmonary, Allergy, Rheumatology Products Briefing Document

Date: July 2, 2013

From: Sofia Chaudhry, MD, Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Through: Susan Limb, MD, Medical Team Leader, DPARP

Through: Badrul Chowdhury, MD, PhD, Director, DPARP

To: Members, Nonprescription Drugs Advisory Committee (NDAC)

Subject: Prescription to OTC switch for (b) (4) (triamcinolone acetonide aqueous nasal spray)

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## 1 Executive Summary

Sanofi Aventis submitted a supplemental NDA application (NDA 20486, Supplement No. 30) on (b) (4), for a prescription (Rx) to nonprescription (over-the-counter; OTC) switch for Nasacort AQ (triamcinolone acetonide aqueous: TAA-AQ), an intranasal corticosteroid spray. While there are multiple prescription intranasal corticosteroid products approved for use in the United States, this is the first proposed Rx to OTC switch for an intranasal corticosteroid.

TAA-AQ was first approved for the treatment of nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 12 years of age and older on May 20, 1996. Use in children 6 to <12 years of age and 2 to <6 years of age was approved on September 26, 2007, and September 19, 2008, respectively. The proposed OTC indication is as follows: “temporarily relieves these symptoms of hay fever or other respiratory allergies (nasal congestion, runny nose, sneezing and itchy nose).” This indication corresponds to the prescription allergic rhinitis indications.

The proposed OTC dosing recommendations match the current prescription doses. The recommended dose for patients 12 years and older is 220 mcg once daily (total daily dose). For children 6 to 12 years, a total daily dose of 110 mcg of TAA-AQ is recommended with instructions to increase to 220 mcg once daily if symptom control is not achieved followed by titration back down to 110 mcg once daily when symptoms are controlled. For children 2 to 6, a total daily dose of 110 mcg of TAA-AQ once daily is recommended.

Dose selection and efficacy for the treatment of allergic rhinitis were established in the pivotal trials conducted in support of the original TAA-AQ prescription product. These results were previously reviewed by the Agency and are summarized in the current product label. The OTC

switch application does not seek any new indications, and no new clinical trial data are included in the supplemental NDA (sNDA).

The safety of TAA-AQ is supported by the clinical development program for the prescription TAA-AQ product in conjunction with postmarketing experience obtained over the past 17 years. Clinical trial data in support of safety include data from the short-term placebo-controlled efficacy and safety trials and 1-year safety trials, as well as assessments of HPA axis effects and pediatric growth. The postmarketing experience encompasses data from the United States and over 60 other countries where TAA-AQ is currently marketed, including data from countries where TAA-AQ is marketed OTC (United Kingdom, Australia, New Zealand, Finland, Malta, Norway, Switzerland, Sweden, Malaysia, and Uruguay).

Current product labeling for intranasal steroids contain class-specific Warnings and Precautions statements regarding the risk of local nasal effects, ocular effects, immunosuppression, alterations in the HPA axis and growth effects. These risks are all described in the current prescription labeling for TAA-AQ. Of these risks, local nasal irritation is the most common adverse effect associated with TAA-AQ. In general, the safety profile for TAA-AQ appears similar to other products in the drug class. While class-specific risks remain a concern, clinically relevant systemic effects or more serious local toxicity from TAA-AQ use appear to occur infrequently.



## 2 Introduction and Regulatory Background

### 2.1 Product Information

Nasacort AQ (Triamcinolone acetonide aqueous [TAA-AQ]) was approved on May 20, 1996, (NDA 20-468) for the treatment of nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older. Supplemental NDAs allowed for the extension of the indication to children 6 to 12 years on September 26, 2007, and in children 2 to 6 years on September 19, 2008. The prescription dosages for each age group are summarized in Table 1. TAA-AQ delivers 55 mcg in each spray, so a 110 mcg total daily dose is equivalent to one 55 mcg spray in each nostril once daily and a 220 mcg total daily dose is equivalent to two 55 mcg sprays in each nostril once daily. In this document, references to the dose refer to the total daily dose (TDD).

**Table 1: Approved TAA-AQ Prescription Dosing**

Age Range (years)	Starting Dose (once daily)	Maximum Dose (once daily)
≥ 12 years of age	220 mcg Two sprays each nostril	220 mcg Two sprays each nostril
6 to 12 years of age	110 mcg One spray in each nostril	220 mcg Two sprays each nostril
2 to 5 years of age	110 mcg One spray in each nostril	110 mcg/day One spray each nostril

A previous formulation of TAA nasal spray was approved on July 11, 1991, as a nasally applied, metered dose aerosol using a chlorofluorocarbon (CFC) propellant. However, due to an international ban on the use of CFC aerosols, the current aqueous formulation was developed and marketed.

TAA-AQ is registered in over 60 countries as a prescription drug and in 10 countries for use without a prescription (UK, Australia, Finland, Malaysia, Malta, New Zealand, Norway, Sweden, Switzerland, and Uruguay).

### 2.2 Currently Available Nonprescription Treatments for Proposed Indications

While intranasal corticosteroids have been available by prescription for the treatment of rhinitis for over 30 years, there are no approved OTC intranasal corticosteroid products in the United States. However, the symptomatic relief of allergic rhinitis is a well-established OTC indication with numerous treatment options.

Over-the-counter products to treat symptoms associated with allergic rhinitis have been available for many years and include both intranasal and oral products: first and second

generation oral antihistamines, oral antihistamine/decongestant combination products, intranasal decongestants, and intranasal cromolyn.

The OTC antihistamines are indicated to temporarily relieve symptoms of allergy and hay fever including sneezing, itchy watery eyes, runny nose and itchy throat. Many of the oral antihistamine products are also marketed in combination with pseudoephedrine or phenylephrine, which adds the relief of nasal congestion to the OTC indication. As such, the proposed indication for TAA-AQ is similar to the approved OTC indication for oral antihistamine/decongestant combination products.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Triamcinolone acetonide is available in multiple formulations in the United States (intranasal, orally inhaled, topical, injectable). Three NDA applications for intranasal TAA have been approved, of which one is currently marketed. None of the intranasal TAA formulations have been withdrawn from the market for safety reasons.

- Nasacort AQ (TAA-AQ; NDA 020-468; approved May 20, 1996): Subject of this sNDA Rx to OTC switch application
- Nasacort HFA (TAA HFA; NDA 020-784; approved April 7, 2004): Approved but not currently marketed
- Nasacort (TAA; NDA 019-798; approved July 11, 1991): Not currently marketed due to the ban on CFC propellant.

### **2.4 Summary of Presubmission Regulatory Activity Related to Submission**

Discussions regarding the overall switch strategy were held on November 29, 2011, and June 18, 2012, between participants from Sanofi-Aventis, the Division of Nonprescription Clinical Evaluation (DNCE), and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Major discussion points are outlined below.

November 29, 2011:

- The OTC indication for TAA-AQ should be consistent with other OTC products used for the treatment of allergic rhinitis.
- The Agency was unaware of any data that support a different risk-benefit profile for children versus adults that would warrant limiting the OTC product to adults. Any such restrictions would require justification in the NDA application.
- The Agency requested that the application include a complete summary of safety, addressing the following issues of interest: local toxicity, HPA axis suppression, growth effects, effects on bone and glucose metabolism, ocular safety, potential drug-drug interactions, and infectious sinusitis.

June 18, 2012

- The Agency provided feedback on the design of the consumer studies.

- As a first-in-class OTC switch, the suitability of marketing TAA-AQ as an OTC product would likely be discussed at an Advisory Committee meeting.

## **3 Review Strategy and Sources of Clinical Data**

### **3.1 Review Strategy**

The OTC switch application does not seek any new indications, and no new clinical trial data were included in the supplemental NDA (sNDA). Clinical trial data to support the dose selection and efficacy and safety of TAA-AQ for the treatment of allergic rhinitis have already been reviewed in detail by the Agency and are summarized in the current approved product label. This review provides a brief summary of data from premarketing clinical trials as well as the clinical trials conducted as postmarketing commitments (PMCs). Section 4 summarizes the efficacy data from the premarketing clinical trials conducted in support of the initial indications. Section 5 summarizes the safety data from the controlled clinical trials with a focus on class-specific risks and includes a high-level overview of available postmarketing data. An additional review of the post-marketing data is provided in the DNCE clinical briefing document. (See page 42.) Section 6 includes a discussion of the overall risk benefit considerations.

Consumer studies for OTC label comprehension and human factors testing are discussed in a separate document included in the briefing package. (See Section 5. Overview of Consumer Studies to Support the Proposed OTC Switch.)

### **3.2 Discussion of Clinical Database and Overview of Post Marketing Safety Database**

A total of 13 trials were conducted to support the initial SAR and PAR indications: 10 trials in adult and adolescent patients  $\geq 12$  years of age and three pediatric trials. Two additional trials were conducted as post marketing commitments. Additional details of these trials are summarized below in Table 2.

In addition to a review of the clinical trial safety database, the sponsor's submission contains a post marketing safety analysis of its internal worldwide pharmacovigilance database from the time of initial approval in 1996 through February 29, 2012. The applicant also conducted a disproportionality analysis of reports from the FDA AERS database (May 1996 through March 31, 2012) and from the WHO VigiBase for all reports submitted by member countries through April 25, 2012. This review presents a high-level summary of the information available from the sponsor's pharmacovigilance database.

**Table 2: Efficacy and Safety Trials**

<b>Trial Number</b>	<b>Objective</b>	<b>Design</b>	<b>Age (yrs)</b>	<b>Treatment (mcg): N<sup>1</sup></b>	<b>Duration</b>	<b>Primary Endpoint</b>
<b>Key Efficacy Trials</b>						
RG5029Y-301 (301)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 70 TAA-AQ 220: 70	2 weeks	Nasal index <sup>2</sup>
RG5029Y-302 (302)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 68 TAA-AQ 220: 68	2 weeks	Nasal index
RG5029Y-304 (304)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 69 TAA-AQ 55: 69 TAA-AQ 220: 68	2 weeks	Nasal index
RG5029Y (305DB) <sup>3</sup>	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 90 TAA-AQ 220: 88	4 weeks	Nasal index
<b>Supportive Efficacy Trials</b>						
RG5029Y-201 (201)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 72 TAA-AQ 27.5: 71 TAA-AQ 55: 72 TAA-AQ 110: 71 TAA-AQ 220: 74	2 weeks	Nasal index
RG5029Y-306 (306)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 102 TAA-AQ 220: 96 BDP <sup>4</sup> : 400	4 weeks	Nasal index
RG5029Y-307 (307)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 43 TAA-AQ 220: 42	22 days	Nasal index
RG5029Y-308 (308)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 99 TAA-AQ 220: 98 TAA-AQ 275 oral: 100	2 weeks	Nasal index
RG5029Y-309 (309)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 142 TAA-AQ 220/110 <sup>5</sup> : 142 TAA-AQ 220/220 <sup>5</sup> : 145	3 weeks	Nasal index
RG5029Y-313 (313)	Efficacy and safety	R, DB, PC, PG	≥ 12	Placebo: 90 TAA-AQ 220: 92	2 weeks	Nasal index
<b>Uncontrolled Long Term Extension</b>						
RG5029Y-305 (305OL) <sup>3</sup>	Safety	OL	≥ 12	TAA-AQ 220: 172	1 year	Safety
<b>Key Pediatric Trials</b>						
RG5029Y-312 (312)	Efficacy and safety	R, DB, PC, PG	6 to 11	Placebo: 76 TAA-AQ 110: 74 TAA-AQ 220: 73	2 weeks	Nasal index
RG5029Y-314 (314)	Efficacy and safety		6 to 11	Placebo: 100 TAA-AQ 110: 105 TAA-AQ 220: 114	12 weeks	Nasal index
XR5029C/3502 (3502DB) <sup>3</sup>	Efficacy and safety	R, DB, PC, PG	2 to 5	Placebo: 238 TAA-AQ 110: 236	4 weeks	TNSS <sup>6</sup>
<b>Pediatric Uncontrolled Long Term</b>						
XR5029C/3502 (3502OL) <sup>3</sup>	Safety	OL	2 to 5	TAA-AQ 110: 428	1 year	Safety
<b>Post Marketing Commitment Trials</b>						
Trica_L_04286	HPA axis		2 to 11	Placebo: 71	6 weeks	Serum

Trial Number	Objective	Design	Age (yrs)	Treatment (mcg): N <sup>1</sup>	Duration	Primary Endpoint
	effects			TAA-AQ 110: 45 TAA-AQ 220: 24		cortisol AUC (0-24 hr)
XRG5029C/3503	Growth effects		3 to 9	Placebo: 148 TAA-AQ 110: 151	1 year	Growth velocity
<sup>1</sup> number randomized in controlled trials or number enrolled in open label extension <sup>2</sup> mean change from baseline in 24-hour nasal index (nasal stuffiness, nasal discharge, and sneezing) <sup>3</sup> trials had double blind and open label extension phase; DB refers to double blind portion, OL to the open label extension <sup>4</sup> BDP = budesonide comparator <sup>5</sup> treatment with TAA-AQ 220 mcg once daily x 1 week followed by 1 week treatment with either TAA-AQ 110 mcg once daily or 220 mcg once daily <sup>6</sup> change from baseline in total nasal symptom score (nasal stuffiness, nasal discharge, sneezing, and itchy nose)						

## 4 Review of Efficacy

### 4.1 Efficacy Summary

The proposed OTC dosing and indication for TAA-AQ are consistent with the dosing and indications approved for the prescription product. The proposed OTC indication is as follows: “temporarily relieves symptoms of hay fever or other respiratory allergies: nasal congestion, runny nose, sneezing and itchy nose.” As no new claims or changes in dosing are proposed, the efficacy data previously submitted in support of the prescription product are adequate to support the proposed OTC TAA-AQ product. No additional trials are required.

The starting and maximum prescription dose for adults and adolescents  $\geq 12$  years of age is 220 mcg once daily, with a recommendation to titrate an individual patient to the minimum effective dose to reduce side effects. In addition, the current prescription product labeling specifically notes that reducing the dose to 110 mcg per day has been shown to be effective in maintaining control of allergic rhinitis symptoms. The proposed OTC dosing corresponds to the prescription dosing.

Current product labeling states that children between 6 and 12 years of age should start on 110 mcg once daily, increase to 220 mcg once daily and subsequently decrease to 110 mcg once daily once control is achieved. Children between 2 and 6 years of age should be treated with 110 mcg once daily. Similar to the adult dosing, the proposed OTC dosing corresponds to the currently approved prescription dosing.

## 4.2 Analysis of Primary Endpoint(s)

### Adult and Adolescents

A total of 1,266 patients ages 12 years and above were included in the controlled clinical trials to support initial approval for adults and adolescents. The primary efficacy endpoint for all of the adult and adolescent trials was the adjusted mean change from baseline in the 24-hour reflective nasal index. The nasal index was defined as the sum of its 3 components: nasal stuffiness, nasal discharge, and sneezing which were scored on a 0 (no symptoms) to 3 scale (severe symptoms). "Itchy nose" was assessed as an additional symptom in a similar manner to the other components.

The primary efficacy data is summarized in Table 3. Replicate statistically significant support for efficacy in the adult and adolescent population was demonstrated by the key efficacy trials (Table 3) with the six supplemental trials providing further support. A similar pattern of efficacy was demonstrated for itchy nose (Table 3) and for the individual components of the nasal index (data not shown).

**Table 3: Premarketing Efficacy Data for Adults and Adolescents ≥ 12 years of age**

Trial	Duration	Treatment group (mcg)	N	Nasal index <sup>1</sup> (SE)	P value vs placebo	Itchy Nose (SE)	P value vs placebo
<b>Key Trials</b>							
301	2 weeks	Placebo	67	-0.94 (0.23)	--	-0.52 (0.09)	--
		TAA-AQ 220	69	-2.83 (0.22)	<0.001	-0.98 (0.09)	<0.001
302	2 weeks	Placebo	68	-1.65 (0.22)	--	-0.59 (0.09)	--
		TAA-AQ 220	68	-2.01 (0.22)	0.131	-0.80 (0.10)	0.06
304	2 weeks	Placebo	62	-1.16 (0.22)	--	-0.53 (0.09)	--
		TAA-AQ 55	58	-1.76 (0.23)	0.030	-0.59 (0.09)	0.322
		TAA-AQ 220	57	-2.56 (0.23)	<0.001	-0.83 (0.09)	0.009
305	4 weeks	Placebo	88	-1.27 (0.18)	--	-0.40 (0.08)	--
		TAA-AQ 220	85	-2.06 (0.18)	0.001	-0.72 (0.08)	0.003
<b>Supplemental Trials</b>							
201	2 weeks	Placebo	72	-1.19 (0.21)	--	-0.53 (0.09)	--
		TAA-AQ 27.5	70	-2.17 (0.21)	<0.001	-0.81 (0.09)	0.011
		TAA-AQ 55	72	-2.27 (0.21)	<0.001	-0.72 (0.09)	0.060
		TAA-AQ 110	70	-1.98 (0.21)	0.004	-0.78 (0.09)	0.044
		TAA-AQ 220	71	-2.53 (0.21)	<0.001	-0.88 (0.09)	0.007



Trial	Duration	Treatment group (mcg)	N	Nasal index <sup>1</sup> (SE)	P value vs placebo	Itchy Nose (SE)	P value vs placebo
306	2 weeks	Placebo	100	-1.42 (0.18)	--	-0.48 (0.07)	--
	2 weeks	TAA-AQ 220	96	-2.93 (0.19)	<0.001	-0.96 (0.07)	<0.001
		Budesonide 400	95	-3.48 (0.19)	<0.001	-1.13 (0.07)	<0.001
307	3 weeks	Placebo	41	-2.36 (0.31)	--	-0.84 (0.13)	--
		TAA-AQ 220	39	-3.54 (0.33)	0.005	-1.09 (0.14)	0.162
308	2 weeks	Placebo	97	-0.85 (0.19)	--	-0.41 (0.08)	--
		TAA-AQ 220	93	-2.66 (0.19)	<0.001	-0.94 (0.08)	<0.001
		TAA 275 oral	97	-1.08 (0.19)	0.384	-0.46	0.639
309	3 weeks	Placebo	111	-1.05 (0.16)	--	-0.39 (0.06)	--
		TAA-AQ 220/110	109	-2.58 (0.16)	<0.001	-0.76 (0.07)	<0.001
		TAA-AQ 220/220	118	-2.94 (0.15)	<0.001	-1.10 (0.06)	<0.001
	Week 2&3 <sup>1</sup>	Placebo	104	-1.25 (0.19)	--	-0.54 (0.07)	--
	Week 2&3	TAA-AQ 220/110	107	-3.04 (0.18)	<0.001	-0.91 (0.07)	<0.001
	Week 2&3	TAA-AQ 220/220	116	-3.42 (0.18)	<0.001	-1.26 (0.07)	<0.001
313	2 weeks	Placebo	89	-1.49 (0.18)	--	-0.52 (0.06)	
		TAA-AQ 220	92	-2.54 (0.18)	<0.001	-0.93 (0.06)	<0.01

Source: modified from module 5.3.5.3 ISE Tables 8 and 17

<sup>1</sup> Nasal index is the sum of nasal stuffiness, nasal discharge, and sneezing scores.

<sup>2</sup> patients in placebo and TAA-AQ 220/220 took same treatment throughout 3 week treatment period; patients in TAA-AQ 110/220 took TAA-AQ 220 for week 1 followed by 110 mcg for next two weeks.

### **Children age 2 to 12 years**

The efficacy for children age 6 to 12 was drawn from three randomized, double-blind, placebo-controlled trials evaluating 518 children ages 6 to 12 years and 464 patients ages 2 to 5. Trial 312 evaluated the efficacy of TAA-AQ for the treatment of SAR in children 6 to < 12 years of age. Trial 314 evaluated TAA-AQ for the treatment of PAR in children 2 to < 12, and Trial 3502 evaluated children 2 to < 6 years of age. Both TAA-AQ 110 mcg and TAA-AQ 220 mcg were studied in children 6 through 12 years of age (312 and 314); only the 110 mcg dose was evaluated for children <6 years of age.

The primary efficacy endpoint for trial 312 and 314 was the change from baseline in 24-hour reflective nasal index. The primary endpoint for trial 3502 was the total nasal symptom score

(TNSS), which has the same symptom components as the nasal index in addition to an assessment of itchy nose.

In both trials, the 110 mcg and 220 mcg dose demonstrated statistically significant differences from placebo in the reflective nasal symptom scoring (nasal index and TNSS, respectively) with similar magnitudes of benefit between the two dosage strengths (Table 4). Trial 3502 evaluated the efficacy of TAA 110 mcg in children 2 through 6 years of age. Statistically significant reductions in 3502 were seen for the 24-hour reflective TNSS compared to placebo (Table 4).

**Table 4: Premarketing Efficacy Data for Children age 2 to < 12 years**

Trial	Duration	Age range (years)	Treatment group (mcg)	N	Nasal index/ TNSS <sup>1</sup> (SE)	P value vs. placebo
312	2 weeks	6 to < 12	Placebo	76	-1.78 (0.20)	--
			TAA-AQ 110	74	-2.62 (0.21)	0.004
			TAA-AQ 220	73	-2.50 (0.21)	0.012
314	4 weeks	2 to < 12	Placebo	100	-1.42 (0.15)	--
			TAA-AQ 110	102	-1.93 (0.15)	0.016
			TAA-AQ 220	113	-1.91 (0.14)	0.020
3502	4 weeks	2 to < 6	Placebo	233	-1.87 (0.15)	--
			TAA-AQ 110	231	-2.31 (0.15)	0.033

Source: modified from module 5.3.5.3 ISE Table 30  
<sup>1</sup>Nasal index (sum of nasal stuffiness, nasal discharge, and sneezing scores for trials 312 and 314. TNSS (sum of sum of nasal stuffiness, nasal discharge, sneezing scores and itchy nose) for trial 3502

## 5 Review of Safety

### 5.1 Safety Summary

The safety of TAA-AQ is supported by the clinical development program for the prescription TAA-AQ product in conjunction with postmarketing experience obtained over the past 17 years. Like all other intranasal corticosteroids, prescription labeling for TAA-AQ contains Warnings and Precautions statements pertaining to the potential risks of corticosteroid use. These risks include the following:

- Local nasal effects
- Increased risk of glaucoma and/or cataracts
- Immunosuppression
- Hypercortisolism and adrenal suppression
- Reduction in growth velocity

Common adverse events associated with TAA-AQ and described in the current prescription label include pharyngitis, epistaxis, flu syndrome, increased cough, bronchitis, dyspepsia, tooth disorder, headache, pharyngolaryngeal pain, nasopharyngitis, abdominal upper pain, diarrhea, and excoriation.



Of the risks described above, local nasal irritation is the most common adverse effect. In clinical trials, local nasal irritation was largely self-limited and did not require medical intervention nor did it result in early discontinuation in most cases. Nasal septal perforation represents a more serious local nasal effect that has been rarely reported postmarketing.

With regards to glaucoma and cataracts, no events occurred in the clinical trials; however, a few cases have been reported in the postmarketing period.

While immunosuppression remains a general concern for corticosteroid use, a safety signal for immunosuppression was not identified in the clinical trial database. Rare cases have been reported in the postmarketing period, although causality could not be confirmed or excluded. Of note, the inadvertent use of TAA-AQ in the setting of acute infectious rhinitis or sinusitis may occur but does not appear to appreciably worsen infection or local toxicity. In general, intranasal corticosteroids are not routinely discontinued in the event of acute sinusitis and various practice parameters include recommendations to use intranasal corticosteroids in the setting of sinusitis.

For the effects on HPA axis, dedicated pharmacodynamic studies in both adults and pediatric patients detected no significant differences between TAA-AQ and placebo groups. These trials are discussed in further detail in the section to follow.

With regards to growth, a dedicated one-year growth trial in prepubescent children age 3 to 9 was conducted by the sponsor. A decrease in growth velocity (-0.45 cm/year) was seen for TAA-AQ, which is similar in magnitude to the growth effect seen in some other intranasal corticosteroid growth studies. The clinical relevance of this finding is unclear. Given the relatively small magnitude of the change, it is unlikely that a clinician could discern such a growth effect in an individual patient that would prompt a change in treatment. From this perspective, the TAA-AQ growth study results are viewed mainly as a sensitive pharmacodynamic assay of systemic exposure.

In general, the safety profile for TAA-AQ appears similar to other products in the drug class. While class-specific risks remain a concern, clinically relevant systemic effects or more serious local toxicity from TAA-AQ use appear to occur infrequently.

## **5.2 Adequacy of Safety Assessments**

From the controlled clinical trials conducted in support of the original NDA, a total of 1,389 adult and adolescent patients were treated with TAA-AQ and a total of 575 patients 2 to 12 years of age were treated with TAA-AQ<sup>1</sup>. In addition to data from the shorter efficacy and safety trials, there are pooled long-term safety data from 203 adult and adolescent patients and 578 pediatric patients 2 to 12 years of age<sup>2</sup>.

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<sup>1</sup> Applicant's pooled database differs slightly from current product label. For consistency, this review will use database outlined in applicant's integrated summary of safety (ISS).

<sup>2</sup> Long term safety for adult and adolescent studies includes data from 305 (DB +OL) + study 901 and from studies 3502 (DB+OL) and 3503

In addition to data provided by the controlled trial database, TAA-AQ has been marketed for 17 years. Sanofi reports that from April 2000 to March 2012 more than 122 million TAA-AQ bottles have been distributed globally, 50 million of which have been distributed in the U.S. Since approval in 1996, there have been 1,396 spontaneous adverse reports for 2,643 adverse events (AEs) with known intranasal TAA-AQ administration. The United States accounted for the greatest percentage of reported cases (86%) followed by Canada (5%), the United Kingdom (3.1%) and Germany (2%). All other countries accounted for  $\leq 1\%$  of the reported cases.

Based on the FDA's Best Pharmaceuticals for Children Act (BPCA) review (2010)<sup>3</sup>, a total of 9.7 million prescriptions were dispensed for the three 12-month periods from November 1, 2006, to October 31, 2009, and pediatric and adolescent patients between the ages of 0 and 16 accounted for approximately 8% (800,000) of these prescriptions.

### **5.3 Submission Specific Safety Concerns**

This section of the review addresses each of the Warnings and Precautions statements carried by all intranasal corticosteroid products. The is followed by discussion of inadvertent use of TAA-AQ in the setting of sinusitis, followed by a discussion of the effects on glucose and bone metabolism since these are well known class effects for corticosteroid products.

#### **Local Nasal Effects**

Current prescription labeling describes a risk of local nasal toxicity, such as epistaxis, nasal septal perforation, candidiasis, and impaired wound healing.

Data from the controlled clinical trials demonstrated a higher rate of epistaxis in adults and adolescents treated with TAA-AQ compared to those treated with placebo ( Table 5). While epistaxis was reported more frequently in children, the rates for TAA-AQ were actually lower than for placebo (Table 5).

Epistaxis was the most frequently report post marketing adverse event with 134 cases reported since 1996.

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<sup>3</sup> Nasacort AQ BPCA Drug Use Review. DHHS, CDER, Office of Surveillance and Epidemiology, January 7, 2010. NDA 20-468.

**Table 5: Local Nasal Effects: Clinical Database<sup>1</sup>**

	Placebo	TAA-AQ
<b>Adults and Adolescents</b>		
N	955	2387
Epistaxis	8 (0.8)	63 (2.6)
Nasal dryness	2 (0.2)	9 (0.4)
Nasal mucosal disorder	0	2 (<0.1)
Nasal cavity mass	0	1 (<0.1)
Nasal edema	0	1 (<0.1)
<b>Pediatric patients 2 to 12</b>		
N	476	644
Epistaxis	32 (6.7)	30 (4.7)
Nasal mucosal disorder	2 (0.4)	2 (0.3)
Nasal edema	0	1 (0.2)
Nasal turbinate abnormality	0	1 (0.2)
Nasal cavity mass	1 (0.2)	0
Nasal dryness	1 (0.2)	0
Nasal ulcer	1 (0.2)	0
Source: ISS Appendix 2.4.10.7.1 and 2.4.10.7.4		
<sup>1</sup> Includes additional data from trials conducted after approval		

The observed occurrence of more serious local toxicity was low and similar to placebo in the controlled premarketing trials for TAA-AQ. One case of nasal septal perforation was reported in an adult patient during a 1-year open label extension trial. Since TAA-AQ's approval in 1996, 13 cases of nasal septal perforation have been reported post-marketing. In addition, the post marketing database includes 2 reports of nasal mucosa atrophy, 2 reports of nasal necrosis, and 6 reports of nasal ulcer.

No cases of nasal candidiasis were reported in the controlled clinical trials. A single case report of fungal rhinitis was reported in the postmarketing database in addition to 8 cases of candidiasis, 4 cases of oral candidiasis, and 3 cases of oral fungal infection.

With regards to impaired local wound healing, there were two reports of delayed wound healing in the postmarketing database, with details provided for one case. However, this case documented a slow healing hand fracture and not impaired healing of an intranasal wound. While it remains possible that the delayed healing of the broken hand was due to global immunosuppression caused by TAA-AQ, it seems unlikely given the limited systemic exposure. As with all post marketing case reports, causality is difficult to determine given the lack of complete information and confounding conditions/medications.

### **Ocular Effects**

Current prescription product labeling discusses an increased risk of cataract or glaucoma associated with corticosteroids in general. No cases of cataract or glaucoma were reported in clinical trials for TAA-AQ. However, postmarketing cases of both glaucoma and cataracts have been reported and are described in the post marketing adverse event section of the product label. A search of Sanofi's internal worldwide post marketing database revealed 20 reported cases of cataracts, 19 of increased intraocular pressure and 6 of glaucoma since 1996.

Again, as with all postmarketing case reports, it is difficult to determine causality to drug or the true incidence of these events given the lack of comparative data.

### **Immunosuppression**

Current prescription labeling contains a general Warnings and Precaution statement regarding the risk of immunosuppression and worsened or reactivated serious infections.

With regards to serious infections in the postmarketing database, 3 cases of fungal infection, 2 cases of pneumonia, 2 cases of histoplasmosis and 1 case each of herpes simplex, herpes zoster, fungal sinusitis and endocarditis have been reported. As with all postmarketing data, it is difficult to determine whether TAA-AQ is the cause of these serious infections given the lack of complete data and information regarding confounding conditions/medications.

No cases of systemic immunosuppression were reported in the premarketing trials.

### **HPA Axis**

Intranasal corticosteroids contain a class-specific Warnings and Precautions statement regarding the potential for adrenal suppression when used at higher than recommended doses and in susceptible individuals.

The effect of TAA-AQ on HPA axis was evaluated in four clinical studies: one in adults, one in children age 6 to 12, one in children age 2 to 5 and one in children age 2 to 11.

In the adult study, no significant difference in six-hour 250 mcg cosyntropin stimulation test was seen between either TAA-AQ 220 mcg or TAA-AQ 440 mcg compared to placebo. Conversely, prednisone 10 mg/day was associated with a significant reduction.

In the study evaluating children 6 to 12 years of age, 80 children received six weeks of TAA-AQ 220 mcg or TAA-AQ 440 mcg. Serum cortisol was then measured thirty and sixty minutes after 250 mcg cosyntropin stimulation. No abnormal response, defined as a peak serum cortisol < 18 mcg/dL, was seen in any pediatric patient after six weeks of dosing of TAA-AQ 440 mcg per day.

HPA axis effects were also evaluated in 61 pediatric patients 2 to 5 years of age; however, the results were inconclusive due to study design flaws (inadequate ACTH stimulation dose).

To better evaluate potential HPA effects in children, the sponsor conducted another study, a 6-week, randomized placebo-controlled trial evaluating the effect of TAA-AQ (110 mcg and 220 mcg) on HPA axis function (as measured by 24-hour serum cortisol AUC) in 140 children (2 to 11 years of age). The study did not demonstrate a significant difference between treatment arms. At the end of week 6, the difference from placebo in the change from baseline in mean serum cortisol AUC<sub>0-24h</sub> was -4.2 mcg•hour/dL (95% CI: -14.7, 6.4).

Overall, these results are similar to the results of HPA axis assessments conducted for other currently marketed intranasal corticosteroid products. Furthermore, no adverse events

associated with adrenal suppression were reported in adults or children in the clinical trials for TAA-AQ.

### **Effect on Growth**

Intranasal corticosteroids carry a class-specific Warnings and Precautions statement regarding a potential reduction in growth velocity in pediatric patients. Previously, a concern regarding intranasal corticosteroids and a possible effect on growth was discussed in 1998 at a joint meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Endocrine and Metabolic Drugs Advisory Committee (EMDAC)<sup>4</sup>. The 1998 meeting centered on the results of an early growth study conducted with a different intranasal corticosteroid, intranasal beclomethasone dipropionate. This trial indicated a difference in growth velocity between beclomethasone and placebo of -1.45 cm/year. The AC panel recommended class labeling for all orally inhaled and intranasal corticosteroid products, identifying the possibility of a decrease in growth velocity.

Since that time, a number of growth studies for other corticosteroid products have been conducted. The Agency has specific guidelines regarding the conduct of these controlled studies<sup>5</sup>. In general, these studies are conducted over the course of at least one year in prepubescent children who are on a stable, linear portion of their growth curves.

It appears that growth studies are quite sensitive as a pharmacodynamic measure of systemic exposure, more sensitive than formal HPA axis studies. A growth study may demonstrate a difference in growth velocity while an HPA study remains negative (i.e., no measurable adrenal suppression). However, the pharmacodynamic effect does not necessarily translate into a clinically relevant change in growth. The magnitude of the difference in growth velocity observed has generally been small, such that it would be difficult to discern a growth effect in any individual patient or prompt a change in treatment.

Data on the long term effects on growth are not entirely consistent across studies or drugs. Some long-term longitudinal studies evaluating orally inhaled corticosteroids, which typically result in higher systemic exposure than their corresponding intranasal formulations, have indicated catch-up growth later in adolescence, with no differences in final adult height,<sup>6,7</sup> while other studies have not.<sup>8</sup> In the Childhood Asthma Management Program (CAMP) study evaluating children who received orally inhaled 400 mcg budesonide daily for 4 to 6 years, a -

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<sup>4</sup> Joint Pulmonary-Allergy Drugs Advisory Committee and Endocrine and Metabolic Drugs Advisory Committee for Orally Inhaled/Intranasal Corticosteroids and Growth in Children, July 30, 1998. Website: <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3430t1.pdf> accessed on June 13, 2013

<sup>5</sup> Guidance for Industry: Orally inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. March 2007.

<sup>6</sup> Agertoft et al; "Effect of Long-Term Treatment with Inhaled Budesonide on Adult Height in Children with Asthma" N Engl J Med 2000; 343:1064-1069.

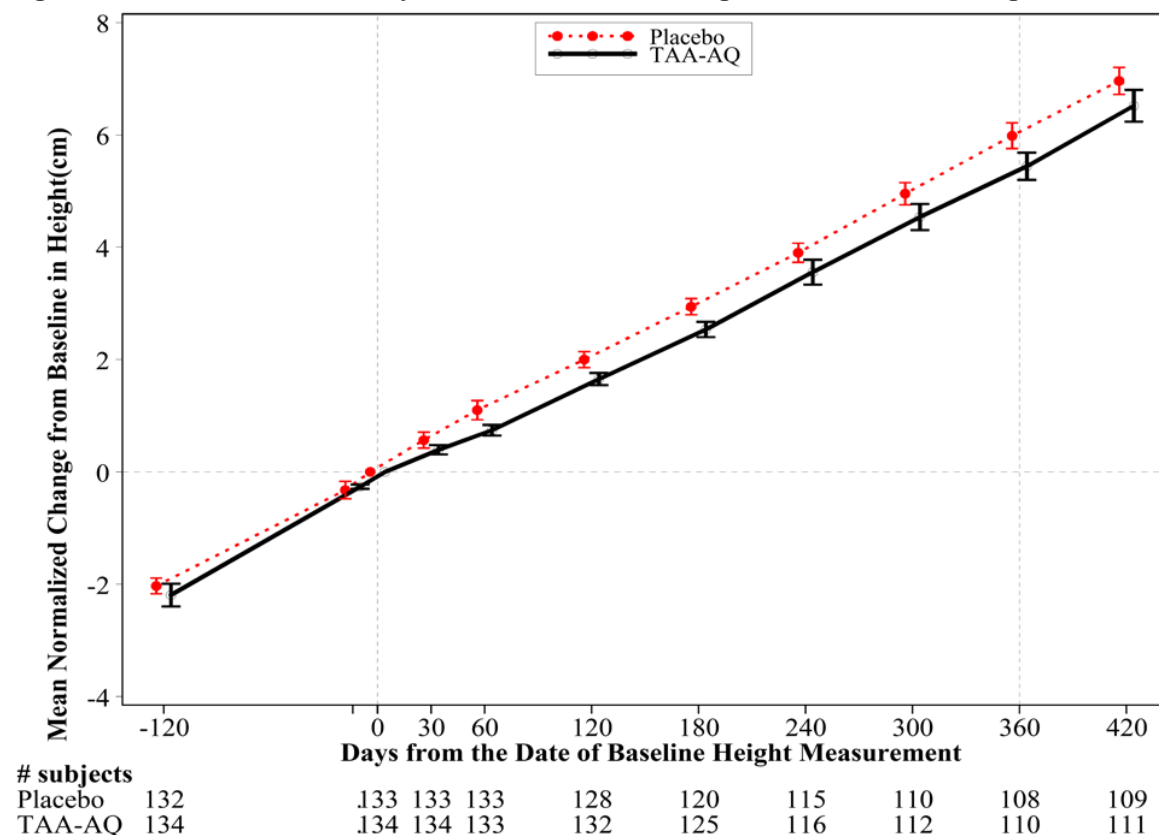
<sup>7</sup> Anthracopoulos et al; "Growth Deceleration of Children on Inhaled Corticosteroids is Compensated for After the First 12 Months of Treatment" Pediatric Pulmonology 2007; 42:465-470.

<sup>8</sup> Kelly et al; "Effect of Inhaled Glucocorticoids in Childhood on Adult Height" N Engl J Med 2012; 367(10): 904-912.

1.2 cm [95% CI (-1.9, -0.5)] difference in adult height was observed and did not appear to be progressive or cumulative.

For TAA-AQ, a dedicated one year growth study was conducted as a postmarketing commitment in 299 prepubescent children age 3 to 9 years with perennial allergic rhinitis. Treatment groups were TAA-AQ 110 mcg once daily and placebo. Growth velocity was estimated for each patient using the slope of the linear regression of height over time as measured by stadiometry. The mean growth velocity was lower in the TAA-AQ group with a difference from placebo of -0.45 cm/year [95% CI (-0.78, -0.11)]. During the follow-up period at 2 months, the mean difference in growth velocity was reversed and actually higher than placebo (+0.7 cm/year). The figure below represents the mean normalized change from baseline in height at each study visit during the one year study.

**Figure 1: TAA-AQ Growth Study: Mean normalized change from baseline in height at each visit**



One-year growth studies have also been conducted for other intranasal corticosteroid products in children, demonstrating a range of effects from +0.61 cm/year to -1.45 cm/year. The results from one-year growth studies for various intranasal corticosteroids are presented in Table 6 for reference.

**Table 6: Growth Study Results of Intranasal Corticosteroids**

Drug	Age (years)	N	Dose (mcg/day)	Δ from placebo (cm/year)	95% CI
Beclomethasone dipropionate <sup>1,2</sup>	6-9.5	100	336	-1.45	not available *
Triamcinolone acetonide aqueous	3-9	299	110	-0.45	- 0.78, -0.11
Budesonide <sup>3</sup>	4-8	229	64	-0.25	-0.59, 0.08
Fluticasone furoate <sup>4</sup>	5-8.5	474	110	-0.27	-0.48, -0.06
Fluticasone propionate <sup>5</sup>	3-9	150	200	-0.14	-0.54, 0.27
Mometasone furoate <sup>2,6</sup>	3-9	82	100	+0.61	0.11,1.10
<p>* p value &lt; 0.01</p> <p><sup>1</sup> Beconase AQ prescribing information accessed May 6, 2013</p> <p><sup>2</sup> Slide 13, “Lessons Learned from Growth Studies with Orally Inhaled and Intranasal Corticosteroids” Joint Dermatologic and Ophthalmic Drugs Advisory Committee with Nonprescription Drugs Advisory Committee, March 24, 2005. Website: <a href="http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4099S1_04_FDA-Wilson_files/frame.htm">http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4099S1_04_FDA-Wilson_files/frame.htm</a></p> <p><sup>3</sup> Rhinocort Aqua prescribing information accessed May 6, 2013</p> <p><sup>4</sup> Veramyst prescribing information accessed May 6, 2013</p> <p><sup>5</sup> Flonase prescribing information accessed May 6, 2013</p> <p><sup>6</sup> Nasonex prescribing information accessed May 6, 2013</p>					

**Sinusitis**

Rates of sinusitis were similar to placebo for patients  $\geq 12$  years (TAA-AQ 1.2% versus placebo 0.8%) and children  $< 12$  years (TAA-AQ 2.0% versus placebo 3.4%) in the controlled clinical trial database. In the postmarketing database 18 cases of sinusitis, including one case of fungal sinusitis, were reported. Causality is difficult to establish given that allergic rhinitis may independently predispose to sinusitis. That being said, intranasal corticosteroids are not routinely discontinued in the setting of acute infectious rhinitis or sinusitis and have been recommended as treatment for acute and chronic rhinitis and sinusitis<sup>9</sup>.

**Effect on Glucose**

An effect on glucose is not specifically included in the product label for TAA-AQ; however, corticosteroids as a drug class are known to potentially impact blood glucose levels.

To address this, the Applicant conducted a search for cases that may be indicative of hyperglycemia or new onset diabetes in its clinical trial database. The search identified a 2 year old patient who developed diabetic ketoacidosis secondary to new onset diabetes in addition to one case each of hunger and dehydration in the pediatric long-term safety study. For the adult and adolescent trials, the search identified 3 cases of thirst in patients receiving TAA-AQ 220 mcg once daily and 1 case of increased weight in a patient receiving an active comparator<sup>10</sup>. The sponsor reports that no additional adverse events were associated with the

<sup>9</sup> Meltzer, E et al; “Rhinosinusitis and Management for the Clinician: A Synopsis of Recent Consensus Guidelines” Mayo Clin Proc. 2011 May; 86(5): 427-443.

<sup>10</sup> Active controlled treatments in this category included: TAA-AQ 275 mcg oral, intranasal Beclomethasone, intranasal budesonide, intranasal fluticasone propionate, and loratadine

cases of increased hunger and dehydration in the pediatric subjects or for the reports of increased thirst in the adult patients. Given the lack of additional symptoms, it is unlikely that these reports represent true cases of hyperglycemia or diabetes. In addition, given the age of the individual with diabetic ketoacidosis, this case is likely a new case of type I diabetes as opposed to an effect of the drug.

In addition to a review of its clinical trial database, the Applicant conducted a similar search of its internal post marketing database. A review of the database since 1996 revealed 8 events of blood glucose increase, 2 events of polyuria, 2 reports of thirst, 1 report of diabetes mellitus inadequate control, 1 report of glycosylated hemoglobin increased, 1 report of hyperglycemia and 1 report of insulin resistance. Overall, these numbers are low, suggesting relatively low risk given the long history and widespread use of the product.

#### **Effect on Bone Metabolism**

Similar to the potential effect on glucose, corticosteroids as a class are known to impact bone metabolism. To address this, the Applicant conducted a search of its clinical trial database and its postmarketing database for potential cases related to alterations in bone metabolism and found one case of osteitis in a subject receiving TAA-AQ 220/110 mcg and one case of exostosis. The postmarketing data revealed 2 cases of bone loss, 1 case of bone formation decreased and 1 case of osteopenia. Overall, these numbers are low given the long history and widespread use of the product.

In addition to the above data, there are two cases of aseptic necrosis reported in the literature in patients taking TAA-AQ 220 mcg. One patient used TAA-AQ QID for one year in addition to as-needed intranasal beclomethasone dipropionate

### **5.4 Common Adverse Events**

Current prescription labeling notes that pharyngitis, epistaxis and increased cough occurred more frequently in the TAA-AQ population in the adult and adolescent clinical trials. In addition to these, flu syndrome, bronchitis, dyspepsia and tooth disorder occurred in more frequently in the TAA-AQ population in children 4 to 12 years of age. In children 2 to 5 years of age, headache, pharyngolaryngeal pain, epistaxis, nasopharyngitis, abdominal upper pain, diarrhea, asthma, rash, excoriation, and rhinorrhea occurred more frequently in the TAA-AQ treatment group.

## **6 Risk-Benefit Analysis**

As the efficacy of TAA-AQ for the proposed indication and age range is well established, the focus of this advisory committee is to determine whether the safety profile for TAA-AQ is appropriate for OTC use.

Of the risks associated with TAA-AQ, local nasal irritation is the most common. Based on the clinical trial safety database and 17 years' postmarketing experience, more serious local



toxicity, including nasal perforations, occurs infrequently. In addition to local nasal effects, an increased risk of glaucoma and cataract is a concern. No glaucoma or cataracts adverse events were seen in the controlled clinical trials and there are relatively few reported cases from the postmarketing period. Corticosteroids as a class are also associated with more serious systemic toxicity, including the potential for alterations of the HPA axis and immunosuppression. While this theoretical risk exists, the data from the clinical trials and post marketing data effects indicate that these occur rarely, if at all, for TAA-AQ. Finally, TAA-AQ, like other intranasal corticosteroids, has been associated with a decrease in growth velocity. Given the limited magnitude of the effect, it is questionable whether it would be possible to discern an effect in an individual patient that would prompt a change in management. From this perspective, the TAA-AQ growth study results are viewed mainly as a sensitive pharmacodynamic assay of systemic exposure.

In general, the safety profile for TAA-AQ appears similar to other products in the drug class. While class-specific risks remain a concern, clinically relevant systemic effects or more serious local toxicity from TAA-AQ use appear to occur infrequently in the proposed age range.

## **4. Overview of Postmarketing Safety and Risk/Benefit Considerations for OTC Use**

### **Division of Non-prescription Clinical Evaluation Briefing Document**

Date: July 2, 2013

From: Steven Osborne MD, Medical officer, DNCE

Through: Lesley Furlong MD, Medical Team Leader, DNCE

Through: Joel Schiffenbauer, MD, Deputy Division Director, DNCE

Through: Shaw Chen MD, Acting Division Director, DNCE

To: Members, Nonprescription Drugs Advisory Committee (NDAC)

Subject: Prescription to OTC switch for (b) (4) (triamcinolone acetonide aqueous nasal spray)

#### ***1. Risk Benefit Assessment for the OTC switch***

The sponsor is proposing the prescription to over-the-counter (Rx-to-OTC) switch of Nasacort AQ nasal spray (triamcinolone acetonide aqueous or TAA-AQ), for the temporary relief of symptoms due to hay fever or other upper respiratory allergies. No new clinical studies have been performed to support the switch application. However, the sponsor conducted consumer studies, including label comprehension and human factors, evaluating the Drug Facts Label (DFL) and Consumer Package Insert (CPI) to support appropriate use of the product in the OTC environment.

Nasacort Nasal Inhaler was first approved in the United States in August 1991 as a nasally inhaled, metered dose aerosol with a chlorofluorocarbon (CFC) propellant. Later, due to the international ban on the use of CFC aerosols, the sponsor developed an aqueous form of triamcinolone acetonide (TAA-AQ, NDA 20-468), with FDA approval on May 20, 1996. From 1996 until the ban on CFC propellants in 2003, the sponsor marketed TAA-AQ (Nasacort AQ) and Nasacort Inhaler (CFC) concurrently, and after July 2003 has marketed just Nasacort AQ.

Nasacort AQ is a microcrystalline suspension of triamcinolone acetonide (TAA) in an aqueous solution indicated for the treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older. The pump-spray is designed to deliver 55 micrograms (mcg) TAA per actuation. TAA is a synthetic fluorinated corticosteroid with approximately 8 times the potency of prednisone in animal models of inflammation.

Since its approval, Nasacort AQ has been available on the market in the United States as a prescription drug for the treatment of nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older. Through supplemental submissions to NDA 20-468, the indication was extended to children 6 to 11 years of age in 1996 and children 2 to 5 years of age in 2007. TAA-AQ has also been registered in over 60 countries as a prescription drug. During the period of April 2001-February 2012, the sponsor distributed 122 million bottles of TAA-AQ worldwide, including 50 million in the United States.

TAA-AQ was first switched to nonprescription in the United Kingdom in 2001 followed by Australia, New Zealand, Finland, Malta, Norway, Switzerland and Sweden. In Malaysia and Uruguay, TAA-AQ was approved for sale without prescription as a pharmacy-only medicine since its first regulatory approval. The lowest age for nonprescription use in these foreign countries ranges from 2 and older in Malaysia and Uruguay, to 12 and older in Australia and New Zealand, and 18 and older in the UK, Norway, and Sweden. The various age restrictions in foreign countries are shown in Table 1 below.

**Table 1. Age restrictions for TAA-AQ use in foreign countries**

Country	mcg/per spray*	Age Restriction	Age Comments
UK	55	18+	“not recommended for children or adolescents under 18 years of age”
Australia	55	12+	“Do not give Telnase to a child under 12 years of age”
Finland	55	18+	Adults (18 years and older)
Malaysia	55	2+	Adults and children 2 years of age and older (same directions for ages 6-12 as draft US label)
Malta	55	18+	“This medicine is not recommended for children or adolescents under 18 years of age”.
New Zealand	55	12+	“Do not give Telnase to a child under 12 years of age”
Norway	55	18+	adults (over 18 years).
Sweden	55	18+	“Children and adolescents below the age of 18 should not be treated with Nasacort”
Switzerland	55	18+	“Enfants et adolescents : l'utilisation de Nasacort Allergo en automédication n'est pas recommandée”. (not recommended in infants and adolescents)
Uruguay	55	2+	Looks same as draft US label (in Spanish) <b>“- Uso pediátrico</b> Niños desde los 6 y hasta los 12 años de edad La dosis recomendada es de 110 mcg, aplicados en 1 pulverización en cada fosa nasal una vez al día. Enpacientes con síntomas de mayor severidad puede indicarse una dosis de 220 mcg una vez al día. Una vez controlados los síntomas, los pacientes deben mantenerse con la mínima dosis efectiva.  Niños de 2 a 5 años La dosis usual recomendada es de 1 pulverización en cada fosa a nasal, una vez al día.

\*1-2 sprays per nostril

Source: sponsor submission

The label comprehension and human factors studies that support the application to switch Nasacort AQ from Rx to OTC examine how consumers interpret the label and how well consumers are able to follow directions for priming, cleaning, and maintenance of the nasal inhaler. The proposed indication and target population is the same as for the prescription product. There is no substantive labeling change proposed for the nonprescription use compared to the prescription, such as a change in warnings or directions for use.

All corticosteroid use has the potential for adverse events; however, the intranasal route of administration of 110-220 mcg of TAA-AQ poses a low overall risk of systemic effects. Argenti et al studied systemic absorption of a 220 mcg intranasal dose of TAA in 24 subjects and found peak plasma concentrations of 0.3-0.4 ng/ml.<sup>1</sup> Derendorf et al found that sustained plasma triamcinolone concentrations greater than 3 ng/ml are associated with potential suppression of the HPA axis.<sup>2</sup>

Considered another way, a sample calculation, assuming 100% systemic absorption of TAA-AQ and 8 times the potency of prednisone, which is a highly permeable or nearly 100% absorbed oral drug, 220 mcg of TAA yields an equivalent of approximately 1.76 mg of prednisone (220 mcg x 8 = 1.76 mg). This is a low dose of prednisone for daily use, but it is not zero. For amounts of absorption of intranasal TAA-AQ less than 100% (e.g. the sponsor mentions 50% absorption), the approximate equivalent dose of prednisone would be correspondingly lower.

The efficacy of Nasacort AQ for the treatment of allergic rhinitis was established through clinical trials.

Allergic rhinitis, stated as “hay fever or other respiratory allergies”, is an established OTC indication, for example with some antihistamines. The major considerations for use of TAA-AQ in the OTC environment are whether the drug can be used safely, potentially for months or years, without a learned intermediary and whether the label can help direct consumers to use the drug correctly, and not misuse it. The main topics to consider are the potential for:

- a suppressive effect on the hypothalamic-pituitary-adrenal axis (HPA axis suppression) with high doses or in susceptible individuals
- a slowing in growth velocity in children
- an impact on adult height if there is a delay in growth velocity in children or adolescents
- immunosuppression and the development or worsening of infections such as tuberculosis, ocular herpes, bacterial, fungal, or parasitic infections

Other potential adverse events are:

- Epistaxis
- Candida (nasal) infection
- Nasal septal perforation
- Effects on bone metabolism

- Effect on glucose metabolism
- Ocular effects (glaucoma or cataracts)
- Psychological or behavioral effects

For this NDA submission, the sponsor performed a label comprehension study and a human factors assessment. FDA agreed that a self-selection study or actual use study were not needed for the submission. The prescription product had two Postmarketing Requirements (PMRs) to study whether use of TAA-AQ in children caused suppression of the hypothalamic-pituitary axis (HPA) or affected the growth velocity of children (“growth study”). These studies are mentioned under Consideration of Special Topics below.

The sponsor’s Integrated Summary of Safety (ISS) included data from:

- Clinical Trials: 43 clinical studies with TAA doses ranging between 27.5-440 mcg/day in 5,558 subjects from age 2 and older, with safety evaluated up to one year of use. The studies include pharmacokinetic studies in healthy subjects, controlled studies which supported the approval of TAA, other controlled studies (efficacy and safety studies for post-approval commitments, Phase IV studies, or studies submitted to foreign regulatory authorities), long-term studies with a treatment duration of 6 months or greater, as well as some other short term studies (single-arm, mixed age or studies which were not performed in subjects with allergic rhinitis)
- Sponsor’s Pharmacovigilance Database: a summary of spontaneously reported safety data from the sponsor’s pharmacovigilance database
- FDA AERS: a summary of the disproportionality analysis performed using Empirica Signal to evaluate reports recorded in the FDA AERS database through the first quarter of 2012
- World Health Organization (WHO): cumulative data released in the second quarter of 2012 in the WHO VigiBase to identify new safety signals
- Literature Review: includes the summary of key safety findings and methodology in the text, and all the safety articles identified are provided as a tabulated summary

In addition, the sponsor submitted a 120-day Safety Update summarizing safety data received after the data lock for the NDA submission.

The primary adverse events noted in postmarketing data are nasal discomfort and congestion, sneezing, alterations of taste and smell, nausea, insomnia, dizziness, fatigue, dyspnea, decreased blood cortisol, cataract, glaucoma, increased ocular pressure, pruritus, rash, and hypersensitivity.

Overall, based on the search for adverse events in the integrated database, the most common adverse event, after drug ineffective, is epistaxis. No new safety concerns for local adverse events such as nasal perforation were observed in the adult/adolescent subjects or the pediatric subjects. Effects on the HPA axis or growth velocity were not reported as treatment emergent adverse events (TEAEs) in the ISS.

## ***2. Clinical Trial Experience***

In 12 studies in adults and adolescent patients (12 to 17 years of age) receiving Nasacort AQ nasal spray 27.5 mcg to 440 mcg once daily, adverse events were reported by 18% of adults 65 years of age or older, 31% of adults 18 to <65 years of age, and 34% of adolescents 12 to <18 years of age. In each age category, subjects treated with placebo reported a similar incidence and type of adverse events, most commonly headache (0-10%), sneezing (1-7.5%), cough (0-3%), and rhinalgia (nasal pain, 0-7.5%). One adult subject who received Nasacort AQ nasal spray reported a nasal septum perforation

A total of 602 children 6 to 12 years of age were studied in 3 double-blind, placebo-controlled clinical trials. Of these, 172 received 110 mcg/day and 207 received 220 mcg/day of Nasacort AQ nasal spray for two, six, or twelve weeks. The longest average durations of treatment for patients receiving 110 mcg/day and 220 mcg/day were 76 days and 80 days, respectively. One percent of patients treated with Nasacort AQ discontinued due to adverse events. No patient receiving 110 mcg/day and one patient receiving 220 mcg/day discontinued due to a serious adverse event. A similar adverse reaction profile was observed in pediatric patients 6-12 years of age as compared to adolescents and adults with the exception of epistaxis, which was reported in less than 2% of the children studied. Adverse reactions from 2 studies in children 4 to 12 years of age receiving Nasacort AQ nasal spray 110 mcg once daily are summarized in Table 2.

A total of 474 children 2 to 5 years of age were studied in a 4-week double-blind, placebo-controlled clinical trial. Of these, 236 received 110 mcg/day of Nasacort AQ nasal spray for a mean duration of 28 days. Adverse reactions from the single placebo-controlled study in children 2 to 5 years of age receiving Nasacort AQ nasal spray 110 mcg once daily are summarized in Table 2 below. No patient discontinued due to a serious adverse event.

For brevity, two examples of treatment emergent adverse events (TEAEs) can be examined:

- 1) Local TEAEs in adults and adolescents in controlled studies.
- 2) TEAEs from long term safety studies in children

*Comments:*

1. *Adults and adolescents are the population of subjects initially studied and they may be the predominant users of an OTC intranasal steroid, and most acute TEAEs will be due local effects.*
2. *Long term use of TAA-AQ in children (e.g., growth effect or other AEs) is possibly the area of most concern for this NDA application.*

Table 2 below shows local TEAEs in controlled studies with adults and adolescent subjects.

**Table 2. Local treatment-emergent adverse events in all controlled studies in adult/adolescent subjects**

Preferred term	Placebo (N=955)	<110 (N=212)	TAA-AQ (mcg)				Total (N=2387)	Other <sup>a</sup> (N=1315)
			110 (N=83)	220 (N=1854)	220/110 (N=238)			
Number (%) of subjects with TEAEs	10 (1.0%)	4 (1.9%)	1 (1.2%)	66 (3.6%)	2 (0.8%)	73 (3.1%)	72 (5.5%)	
Epistaxis	8 (0.8%)	4 (1.9%)	1 (1.2%)	57 (3.1%)	1 (0.4%)	63 (2.6%)	61 (4.6%)	
Nasal dryness	2 (0.2%)	0	0	8 (0.4%)	1 (0.4%)	9 (0.4%)	6 (0.5%)	
Nasal mucosal disorder	0	0	0	2 (0.1%)	0	2 (<0.1%)	2 (0.2%)	
Nasal cavity mass	0	0	0	1 (<0.1%)	0	1 (<0.1%)	0	
Nasal oedema	0	0	0	1 (<0.1%)	0	1 (<0.1%)	2 (0.2%)	
Nasal mucosal hypertrophy	0	0	0	0	0	0	1 (<0.1%)	
Nasal ulcer	0	0	0	0	0	0	5 (0.4%)	

Adverse events were coded using MedDRA version 14.1.

Note: Subjects are counted only once per preferred term. The numbers within a column may not add to the total number of subjects with at least one TEAE, since a subject may have had more than one TEAE. Preferred terms are sorted by decreasing frequency of TAA-AQ total group.

<sup>a</sup> Active controlled treatments include TAA-AQ 275 mcg oral, beclomethasone (Beconase), budesonide (Rhinocort), fluticasone (Flonase), and loratadine (Claritin).

Source p118 of 7658 sponsor's submission

Table 3 below shows TEAEs in long-term safety studies of pediatric subjects.



**Table 3. Summary of treatment-emergent adverse events in long-term safety studies in pediatric subjects ages 2 to < 12 years of age**

<b>Primary system organ class Preferred term n(%)</b>	<b>Placebo (N=148)</b>	<b>TAA-AQ 110 mcg (N=578)</b>
Number (%) of subjects with TEAEs	114 (77.0%)	442 (76.5%)
Infections and infestations	77 (52.0%)	306 (52.9%)
Nasopharyngitis	18 (12.2%)	84 (14.5%)
Upper respiratory tract infection	19 (12.8%)	63 (10.9%)
Sinusitis	11 (7.4%)	39 (6.7%)
Ear infection	7 (4.7%)	35 (6.1%)
Otitis media	9 (6.1%)	34 (5.9%)
Viral infection	3 (2.0%)	34 (5.9%)
Pharyngitis streptococcal	10 (6.8%)	29 (5.0%)
Nervous system disorders	34 (23.0%)	87 (15.1%)
Headache	31 (20.9%)	75 (13.0%)
Respiratory, thoracic and mediastinal disorders	63 (42.6%)	249 (43.1%)
Cough	30 (20.3%)	122 (21.1%)
Oropharyngeal pain	18 (12.2%)	52 (9.0%)
Epistaxis	7 (4.7%)	41 (7.1%)
Rhinorrhoea	9 (6.1%)	39 (6.7%)
Asthma	10 (6.8%)	36 (6.2%)
Nasal congestion	11 (7.4%)	30 (5.2%)
Gastrointestinal disorders	28 (18.9%)	114 (19.7%)
Vomiting	8 (5.4%)	55 (9.5%)
Abdominal pain upper	15 (10.1%)	39 (6.7%)
Skin and subcutaneous tissue disorders	16 (10.8%)	63 (10.9%)
Rash	4 (2.7%)	29 (5.0%)
General disorders and administration site conditions	43 (29.1%)	148 (25.6%)
Pyrexia	38 (25.7%)	133 (23.0%)

Adverse events were coded using MedDRA version 14.1.

Presented are TEAEs that occurred in at least 5% of subjects in TAA-AQ treatment group.

Note: Subjects are counted only once per preferred term as well as per system organ class. The numbers within a column may not add to the total number of subjects with at least one TEAE (under a system organ class), since a subject may have had more than one TEAE. System organ classes are sorted in internationally agreed order.

Preferred terms within a system organ class are sorted by decreasing frequency of the TAA-AQ group.

Table 3 includes subjects from Studies XRG5029C/3502 (DB+OL) and XRG5029C/3503.

Source: sponsor submission, page 60 of Integrated Summary of Safety

*Comments: Table 2 shows that epistaxis was reported in 63 of 2387 subjects (2.6%), with 57 of the 63 subjects using 220 mcg TAA-AQ. These data may suggest that epistaxis is more likely with higher doses of TAA-AQ.*

*Table 3 shows that in long term safety studies involving 578 pediatric subjects treated with TAA-AQ and 148 treated with placebo, the most common TEAE or symptoms in children age 2 to <12 years of age are upper respiratory infections, headache, and fever. However, these adverse events are common in children and they were reported at similar incidence in the TAA-AQ and placebo group.*

### **3. Postmarketing Experience**

The sponsor analyzed safety data from the Sanofi-aventis pharmacovigilance database, the FDA AERSs database, and WHO Vigibase reporting systems using data mining methods to identify unusual or unexpected product-event combinations warranting further investigation. They did a disproportionality analysis using Empirica Signal™ evaluating reports recorded in the FDA AERS database through the first quarter of 2012 and in the WHO VigiBase using cumulative data released in the second quarter of 2012. The Sanofi-aventis pharmacovigilance database includes adverse event reports it received through February 29, 2012.

Adverse events identified during post-approval use of Nasacort AQ from all sources include: nasal discomfort and congestion, sneezing, alterations of taste and smell, headache, nausea, insomnia, dizziness, fatigue, dyspnea, cataract, glaucoma, increased ocular pressure, pruritus, rash, and hypersensitivity. However, not all of these AEs are necessarily due to use of Nasacort AQ.

#### FDA AERS database

The sponsor notes that its disproportionality analysis in the FDA AERS database identified no new signals warranting further investigation in the period when TAA-AQ formulation has been available on the US market. Most events identified as signal of disproportionate reporting in the FDA AERS database from 1996 are either labeled, or considered as indication related, or have been analyzed as AEs in other documents of this submission.

#### WHO database

The sponsor notes that its disproportionality analysis of non-US reports in the WHO VigiBase also identified no new safety signals in the period when TAA-AQ formulation has been available on the market or in the other time periods considered.

#### Sanofi-aventis Global Pharmacovigilance database

The sponsor submitted 16 years of data from its Global Pharmacovigilance database. A total of 1,396 spontaneous reports involving 2,643 AEs received by Sanofi-aventis from worldwide sources were reported with use of Nasacort AQ. These reports were most commonly received from the United States (2242), Canada 144) and the UK (83). In addition, 609 spontaneous reports involving 1,352 AEs were received for TAA-intranasal, not otherwise specified (e.g., where the currently marketed drug product formulation TAA-AQ or TAA-CFC cannot be further differentiated). The AE totals from various TAA products are summarized in Table 4 below.

**Table 4. Categories of triamcinolone acetonide AE reports**

Category	No. of spontaneous cases	Total No. of AEs
1.) (Nasacort-AQ )	1396	2643
2.) TAA-Intranasal NOS	609	1352
3.) TAA-NOS	31	40
<b>Total</b>	<b>2036</b>	<b>4035</b>

Source: sponsor's Postmarketing analysis of internal database, page 15.

NOS = not otherwise specified

TAA-Intranasal NOS: product not be confirmed from AE forms as either Nasacort AQ or Nasacort Inhaler (CFC)

TAA-NOS refers to an unknown TAA formulation and unknown route of administration (e.g., could be nasal, oral or topical)

The AEs are differentiated by MedDRA preferred term for Nasacort AQ (2643 total AEs) in Table 5 below. For TAA-AQ, the most frequently reported AEs were drug ineffective, epistaxis, and headache, which are in the prescription label. Reports involving serious adverse events (SAEs) accounted for 7% of all spontaneous reports.

**Table 5. Nasacort AQ AEs by MedDRA term**

MedDRA Preferred Term	No. (%) of AEs		
	Serious	Non-serious	Total
<b>Total adverse events</b>	<b>201 (7.6)</b>	<b>2442 (92.4)</b>	<b>2643</b>
<b>Total case reports</b>	<b>98 (7.0)</b>	<b>1329 (95.2)</b>	<b>1396*</b>
Drug ineffective	0 (0.0)	281 (10.6)	281 (10.6)
Epistaxis	7 (0.3)	127 (4.8)	134 (5.1)
Headache	3 (0.1)	117 (4.4)	120 (4.5)
Nasal discomfort	2 (0.1)	79 (3.0)	81 (3.1)
Dizziness	4 (0.2)	66 (2.5)	70 (2.6)
Nasal congestion	2 (0.1)	53 (2.0)	55 (2.1)
Dysgeusia	0 (0.0)	41 (1.6)	41 (1.6)
Oropharyngeal pain	0 (0.0)	41 (1.6)	41 (1.6)
Anosmia	3 (0.1)	34 (1.3)	37 (1.4)
Nausea	4 (0.2)	32 (1.2)	36 (1.4)
Rhinorrhoea	0 (0.0)	36 (1.4)	36 (1.4)
Cough	1 (0.0)	34 (1.3)	35 (1.3)
Hypersensitivity	8 (0.3)	26 (1.0)	34 (1.3)
Insomnia	0 (0.0)	33 (1.2)	33 (1.2)
Parosmia	0 (0.0)	32 (1.2)	32 (1.2)
Rash	1 (0.0)	28 (1.1)	29 (1.1)
Ageusia	2 (0.1)	24 (0.9)	26 (1.0)

Source: Sponsor Postmarketing analysis of internal database, page 19

\*Note: The case total is not additive, as a single case may contain both serious and non-serious events.

*Comments: Table 5 shows that the most frequently reported AEs by MedDRA Preferred Term for Nasacort AQ were drug ineffective, epistaxis, and headache, which are largely local effects, although 7 of the epistaxis cases were reported as serious. Likely, this means the affected patients with epistaxis needed medical intervention, which also happens for other causes of epistaxis in the general population*

Also, as seen in Table 5 above, 98 spontaneous Nasacort AQ cases reported 201 serious adverse events (SAEs). These are shown in Table 6 below, which classifies the serious spontaneous cases according to the serious criterion reported in the case. Of note, there was one fatal case report of a patient who died from metastatic gallbladder cancer, post completion of a Nasacort AQ clinical trial; however, this fatal case was assessed as not related to TAA-AQ.

**Table 6. Most frequently reported SAEs for Nasacort AQ**

MedDRA PT	No. (%) of SAEs
<b>Total AEs</b>	<b>2643</b>
<b>Total SAEs</b>	<b>201 (7.6)</b>
<b>Total case reports</b>	<b>98</b>
Cataract	14 (0.5)
Nasal septum perforation	13 (0.5)
Hypersensitivity	8 (0.3)
Epistaxis	7 (0.3)
Dyspnoea	5 (0.2)
Anaphylactic reaction	5 (0.2)
Dizziness	4 (0.2)
Nausea	4 (0.2)
Decreased appetite	4 (0.2)

Source: Sponsor Postmarketing analysis of internal database, page 20

The sponsor totaled the most frequently reported SAEs as a percentage of the 3995 total AEs for all TAA intranasal products (2643 Nasacort AQ+ 1352 TAA-NOS from Table 4) which yielded cataract (0.5%), nasal septum perforation (0.5%), hypersensitivity (0.3%), and epistaxis (0.3%), as the most common reported adverse events. Considering the 1352 AEs from the TAA-NOS reports, no additional signals were noted.

### Published Literature

The sponsor reviewed safety literature from 1970 through 19 July 2012 and concluded that the literature reports reflected the known safety profile for TAA-AQ and the current drug label. Of interest, in reviewing literature related to special topics (see discussion below); two cases of aseptic necrosis of the hip were reported in individuals with previous or concurrent use of corticosteroids, who used TAA-AQ in excess of that recommended in label. Separately, no cases of drug-drug interactions with TAA-AQ and CYP3A4 inhibitors were identified.

*Comment: This report does not present any new, serious unlisted reactions not yet included in the current prescription label for triamcinolone acetonide.*

### Safety Update

The sponsor provided a safety update of all spontaneous reports it received from March 1, 2012-December 13, 2012, and an updated analysis of the FDA AERS and WHO Vigibase databases including the last quarterly releases from these external databases, and a review of the literature covering the period from July 20, 2012 through January 18, 2013. The

sponsor estimates that about 5 million bottles of Nasacort AQ were distributed globally during this time.

The sponsor received 37 spontaneous reports involving 66 adverse events, including 7 SAEs reported by consumers. Five SAEs included glaucoma, nasal septum perforation, convulsion, and disease recurrence (“sinus problems”). There were no AEs associated with a fatal outcome. In addition to the above-mentioned five SAEs, there were two SAEs reported with an unknown formulation of TAA; namely, anaphylactic reaction and Cushing’s. It was not clear from the case descriptions whether the patient received TAA-AQ. These adverse events are shown in Table 7 below. The AEs reported most frequently to the sponsor from March 1-December 13, 2012 included drug ineffective, dizziness, headache, and nausea.

**Table 7. Reported adverse events March 1-December 13, 2012 for Nasacort AQ by MedDRA preferred term**

MedDRA Preferred term	Serious	Non-serious	Total
<b>Total adverse events</b>	<b>7 (10.6)</b>	<b>59 (89.4)</b>	<b>66</b>
<b>Total case reports</b>	<b>6 (16.2)</b>	<b>31 (83.8)</b>	<b>37</b>
Drug ineffective	0 (0.0)	5 (7.6)	5 (7.6)
Dizziness	0 (0.0)	4 (6.1)	4 (6.1)
Headache	0 (0.0)	3 (4.5)	3 (4.5)
Nausea	0 (0.0)	3 (4.5)	3 (4.5)
Back pain	0 (0.0)	2 (3.0)	2 (3.0)
Glaucoma	2 (3.0)	0 (0.0)	2 (3.0)
Influenza like illness	0 (0.0)	2 (3.0)	2 (3.0)
Nasal congestion	0 (0.0)	2 (3.0)	2 (3.0)
Abdominal discomfort	0 (0.0)	1 (1.5)	1 (1.5)
Anaphylactic reaction*	1 (1.5)	0 (0.0)	1 (1.5)
Balance disorder	0 (0.0)	1 (1.5)	1 (1.5)
Cardiac discomfort	0 (0.0)	1 (1.5)	1 (1.5)
Coeliac disease	0 (0.0)	1 (1.5)	1 (1.5)
Convulsion	1 (1.5)	0 (0.0)	1 (1.5)
Cushing's syndrome*	1 (1.5)	0 (0.0)	1 (1.5)
Disease recurrence**	1 (1.5)	0 (0.0)	1 (1.5)
Ear congestion	0 (0.0)	1 (1.5)	1 (1.5)
Ear pain	0 (0.0)	1 (1.5)	1 (1.5)
Epistaxis	0 (0.0)	1 (1.5)	1 (1.5)
Eye disorder	0 (0.0)	1 (1.5)	1 (1.5)

MedDRA Preferred term	Serious	Non-serious	Total
Fatigue	0 (0.0)	1 (1.5)	1 (1.5)
Head discomfort	0 (0.0)	1 (1.5)	1 (1.5)
Heart rate increased	0 (0.0)	1 (1.5)	1 (1.5)
Hyperhidrosis	0 (0.0)	1 (1.5)	1 (1.5)
Hypertension	0 (0.0)	1 (1.5)	1 (1.5)
Incorrect route of drug administration	0 (0.0)	1 (1.5)	1 (1.5)
Intraocular pressure increased	0 (0.0)	1 (1.5)	1 (1.5)
Lethargy	0 (0.0)	1 (1.5)	1 (1.5)
Mouth ulceration	0 (0.0)	1 (1.5)	1 (1.5)
Mucosal pigmentation	0 (0.0)	1 (1.5)	1 (1.5)
Multiple allergies	0 (0.0)	1 (1.5)	1 (1.5)
Musculoskeletal stiffness	0 (0.0)	1 (1.5)	1 (1.5)
Nasal discomfort	0 (0.0)	1 (1.5)	1 (1.5)
Nasal disorder	0 (0.0)	1 (1.5)	1 (1.5)
Nasal septum perforation	1 (1.5)	0 (0.0)	1 (1.5)
Neck pain	0 (0.0)	1 (1.5)	1 (1.5)
Nervousness	0 (0.0)	1 (1.5)	1 (1.5)
Oral fungal infection	0 (0.0)	1 (1.5)	1 (1.5)
Overdose	0 (0.0)	1 (1.5)	1 (1.5)
Pyrexia	0 (0.0)	1 (1.5)	1 (1.5)
Rash	0 (0.0)	1 (1.5)	1 (1.5)
Rhinitis	0 (0.0)	1 (1.5)	1 (1.5)
Sensitivity of teeth	0 (0.0)	1 (1.5)	1 (1.5)
Sinus disorder	0 (0.0)	1 (1.5)	1 (1.5)
Therapeutic response decreased	0 (0.0)	1 (1.5)	1 (1.5)
Therapeutic response unexpected	0 (0.0)	1 (1.5)	1 (1.5)
Tongue disorder	0 (0.0)	1 (1.5)	1 (1.5)
Tooth discolouration	0 (0.0)	1 (1.5)	1 (1.5)
Unevaluable event	0 (0.0)	1 (1.5)	1 (1.5)
Urine amphetamine positive	0 (0.0)	1 (1.5)	1 (1.5)
Wrong technique in drug usage process***	0 (0.0)	1 (1.5)	1 (1.5)

Source: sponsor's 120-day safety update report, page 16

Table 8 below shows the individual SAEs from Table 7.

**Table 8. Reported SAEs March 1-December 13, 2012 for Nasacort AQ by MedDRA preferred term**

MedDRA Preferred term	No. (%) of SAEs
<b>Total adverse events</b>	<b>66</b>
<b>Total serious adverse events</b>	<b>7 (10.6)</b>
<b>Total case reports</b>	<b>6 (16.2)</b>
Glaucoma	2 (3.0)
Anaphylactic reaction*	1 (1.5)
Convulsion	1 (1.5)
Cushing's syndrome*	1 (1.5)
Disease recurrence**	1 (1.5)
Nasal septum perforation	1 (1.5)

Source: sponsor's 120-day safety update report, page 17

\* PTs reported in cases of unknown TAA formulation administration

\*\*"Sinus problems" was reported as Disease recurrence

Brief case histories for the nasal septal perforation and the 2 cases of glaucoma are shown in the section Considerations of Special Topics, below.

*Comment: The case histories regarding glaucoma are brief, but show that in the prescription environment reports of adverse events such as nasal septal perforation and glaucoma do occur. In the report of nasal perforation, the consumer experienced a nosebleed and presented to the doctor. In the 2 reports of glaucoma, consumers did not apparently report symptoms but were ages 63 and 84, when glaucoma is more likely to occur.*

#### **4. Consideration of Special Topics**

##### **HPA axis suppression**

\_\_\_The sponsor concludes that, based on the results from its PMR study and a search for AEs in the integrated database, no evidence of clinically relevant HPA axis suppression was observed in the adult/adolescent subjects or the pediatric subjects. Serum cortisol over an integrated 24-hour period was not suppressed. The DPARP review team discusses this topic in more detail in their 5 *Review of Safety*. In addition, the research by Argenti et al and Derendorf, et al., is discussed above along with a sample calculation of an approximate prednisone-equivalent (1.76 mg or less) of the proposed maximum daily dose of 220 mcg of TAA-AQ.

*Comment: Suppressive effect on the HPA axis seems unlikely with labeled use of TAA-AQ.*



### Growth Effects

The prescription label includes a Precaution about potential growth retardation in children and a recommendation to use the lowest dose at which effective control of symptoms is maintained. To assess growth effects, the sponsor performed a growth velocity study as a PMR, and evaluated TEAEs associated with growth effects by searching its integrated safety database with MedDRA preferred terms of growth retardation or abnormal bone development. Based on these data no evidence of TEAEs related to growth was observed in the adolescent subjects or the pediatric subjects, although the growth velocity study showed a slowing of growth velocity. The study also showed that the effects on growth were reversed during a year of follow-up when subjects did not use TAA-AQ. However, long term effects with continuous, chronic use of TAA-AQ are unknown. The DPARP review team discussed this topic in more detail in their 5 *Review of Safety*.

*Comment: The data on growth velocity effects with TAA-AQ are somewhat limited: growth is slowed during one year of use with recovery in the following year during non-use. We do not have data on what happens with multi-year use during the growing stages, nor how various periods of non-use might affect growth rates.*

### Bone Metabolism

The sponsor notes that only one of 2387 subjects treated with TAA-AQ and one of 1315 subjects treated with an active comparator and none of 955 subjects in placebo group reported a TEAE associated with bone metabolism. For exposure to TAA-AQ 220 mcg, 1 subject (<0.1%) reported an osteitis, which involved a jaw inflammation of moderate intensity. The subject recovered without sequelae and a relationship to TAA-AQ was not established.

*Comment: An effect on bone metabolism seems unlikely with labeled use of TAA-AQ; however, if the drug is used concomitantly with other corticosteroid drugs, it could contribute to osteopenia or other AEs related to bone metabolism.*

### Glucose Metabolism

The sponsor found no clinically relevant evidence of TEAEs affecting glucose metabolism in the adult/adolescent subjects, based on data from its integrated database. In long-term studies with pediatric subjects, 0.5% of subjects (3 of 578) exposed to TAA-AQ 110 mcg reported symptoms that could be indicative of an effect on glucose metabolism. One subject a two-year old white male presented diabetic ketoacidosis (DKA) which the investigator considered not related to the study medication. Two other subjects reported increased appetite and dehydration, respectively, but had a normal glucose.

*Comment: An effect on glucose metabolism seems unlikely with labeled use of TAA-AQ; however, if the drug is used concomitantly with other corticosteroid drugs, it could contribute to an effect on glucose metabolism.*

### Ocular Safety

The sponsor searched its *clinical trials integrated safety database* for ocular TEAEs and found facial pain, blurred vision, eye pain, ocular hyperemia and photophobia, but no reports of glaucoma or cataracts.

However, in its *postmarketing safety database*, the sponsor received reports of 14 ocular cases from healthcare professionals and 27 ocular cases from consumers. These 41 cases reported 48 ocular AEs including 20 cataracts, 19 intraocular pressure increased, 6 glaucoma, 2 ocular hypertension, and 1 open angle glaucoma. These events represent 1.8% (48/2643) of total adverse events for Nasacort AQ, with cataracts 0.8%, intraocular pressure increased 0.7%, glaucoma 0.2%, ocular hypertension <0.1%, and open angular glaucoma <0.1%. A cause and effect relationship with use of TAA-AQ cannot be established, as these ocular conditions occur naturally; however, oral corticosteroids are associated with subcapsular cataracts and can lead to increased intraocular pressure and glaucoma. No new safety concerns for ocular safety were observed in the adult/adolescent subjects or the pediatric subjects. Two cases of glaucoma are illustrated below.

#### **Glaucoma (2 cases):**

Case 2012SA025200 is a consumer report that involves a 63-year-old male who was taking Nasacort AQ once or twice daily intranasal as needed for sinusitis and chronic rhinitis for five years. For the past three years, the patient had a glaucoma check and his number was high (between 50-70). He was not being treated for glaucoma. Therapy with Nasacort AQ was ongoing.

Case 2012SA085710, is a consumer report that involves an 84-year-old female with a history of mercury poisoning and allergy to mercury. She initiated intranasal Nasacort and phenylephrine (4 Way Mentholated Nasal Spray) 2 squirts every night for about 5 years. In 2011, she developed glaucoma. The phenylephrine nasal spray was used under medical advice for sinus problems, but it was unknown if the dosage was recommended. She reported that her doctor gave her Nasacort, which gave her glaucoma. She further stated that she started to have sinus problems again (disease recurrence) for the first time in years. Therapy with phenylephrine was discontinued and the action taken with Nasacort was unknown. At the time of the report, the glaucoma and return of sinus problems (disease recurrence) were ongoing. Concomitant medications were unknown and no additional information was provided. The prescription label includes a Precaution about glaucoma and/or cataracts with a recommendation for close monitoring in patients with a history of these conditions or a change

in vision. The Precaution is based on known effects of systemic steroids and some absorption is possible with intranasal steroids.

*Comment: In the OTC setting, the potential for glaucoma or cataract worsening in older patients will need to be addressed in labeling recommendations.*

### Infectious Sinusitis

The most common event for sinus-related symptoms is sinusitis, not otherwise specified. No new safety concerns for infectious sinusitis were observed in the adult/adolescent subjects or the pediatric subjects. The TEAEs observed in this category are consistent with the label for Nasacort AQ.

*Comment: Fungal growth, such as growth of Candida, may be stimulated by a corticosteroid, but an affected patient will experience local symptoms and will probably discontinue the drug or consult a doctor.*

### Local Adverse Events: Perforated Nasal Septum and Epistaxis

Epistaxis was reported in 2.6% subjects in the total TAA-AQ group, in 4.6% subjects in subjects exposed to other active comparators, and in 0.8% subjects exposed to placebo. Nasal dryness was observed at a similar rate in the total TAA-AQ group, other active comparators group and the placebo group (0.4%, 0.5% and 0.2% respectively). Nasal mucosal disorder (2 subjects), nasal cavity mass (1 subject) and nasal edema (1 subject) were reported in the TAA-AQ 220 mcg group. Nasal ulcers (5 of 1315, 0.4%) were reported with other active comparators and were not presented with any dose of TAA-AQ. A case of nasal septal perforation is shown below.

#### **Nasal septum perforation:**

Case 2012SA063666, is a consumer report that involves a 61-year-old female who received TAA-AQ and experienced “a raging infection in her head and her nose was bleeding a lot.” The patient stated that she directed the spray straight into her nose, and not toward her septum. However, an otolaryngologist diagnosed a hole in her septum. Treatment with TAA-AQ was discontinued. No information about the duration of TAA-AQ was provided. The hole in her septum was ongoing; however, she was scheduled for surgery in September 2012 to repair the perforation. No additional follow-up information was received and the report was not substantiated by a HCP.

*Comment: The occurrence and the treatment of nasal septum perforation are likely to be similar with labeled use of Nasacort AQ in the Rx or OTC environment.*

Other labeling considerations:

The sponsor's label should inform consumers about proper self-selection and potential adverse events (e.g., growth delay, even if a small amount).

Label considerations include:

- *Pregnancy*: the sponsor's TAA-AQ is a Pregnancy Category C drug. On the prescription label the *Warning* about use in pregnancy says Pregnancy Category C, "...should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus". In other instances for OTC drugs, the Drug Facts Label reflects a Pregnancy Category C drug by "**If pregnant or breast-feeding** ask a health professional before use".
- *Chronic Use*: Other OTC labels address concerns for chronic use with the following language: "use for the shortest time possible to control symptoms"

## **5. Summary**

In summary, in the prescription environment, TAA-AQ has a favorable risk-benefit profile for the treatment of seasonal and perennial allergic rhinitis. This drug is a good candidate for the treatment of SAR and PAR in the OTC environment. The terms SAR and PAR are not necessarily known to OTC consumers, so the sponsor proposed terms such as hay fever and other respiratory allergies and typical symptoms of hay fever for the label. Of note, these terms appear on labels for OTC antihistamines.

The common adverse events seen with TAA-AQ are mostly local adverse events such as nasal stinging and nosebleeds, which can be addressed through the label. Serious events have been reported infrequently with TAA-AQ, including cataracts, glaucoma, nasal septum perforation, hypersensitivity, and epistaxis, at a rate of 0.5% or less, based on total AEs for all of the sponsor's TAA products since approval in 1996. Rarely, elevated intraocular pressure and cataracts, known effects of oral corticosteroids, have been reported. A safety literature search reflected the known safety profile of TAA-AQ consistent with the prescription label. Review of the postmarketing safety databases and analysis of the FDA/AERS and WHO safety databases did not raise new signals.

For any concerns about how the Drug Facts Label alone can communicate about adverse events or provide adequate information under the Warnings or Directions sections of the DFL, a Consumer Leaflet might help convey the information in a more complete manner.

## References

1. Argenti D et al. Nasal mucosal inflammation has no effect on the absorption of intranasal triamcinolone acetonide. *J Clin Pharmacol*, 1994 Aug; 34(8):854-8.
2. Derendorf et al. Pharmacokinetics and pharmacodynamics of glucocorticoid suspension after intraarticular administration. *Clin Pharmacol Ther* 1986; 39:313-7.

## 5. Overview of Consumer Studies to Support the Proposed OTC Switch

The Sponsor fielded three consumer studies in support of the proposed OTC switch of Nasacort AQ:

- Label Comprehension Study Assessing the Growth Statement
- Label Comprehension Study (LCS) Assessing the Drug Facts Label (DFL) and the Consumer Package Insert (CPI)
- Human Factors Study Assessing Pump Preparation for Efficacious Use

These studies are discussed below.

### ***Label Comprehension Study (LCS) for Growth Text (#2012025)***

#### **A. Background**

In June 2012, FDA advised the Sponsor that labeling language needed to reflect the results of the growth study. The Sponsor conducted iterative qualitative research for label development; the resulting proposed growth language has two components: 1) a direction to tell the child's doctor about use of the product and 2) an informational statement about the potential growth effects in children.

#### **B. Objectives**

The overall objective was to test consumer comprehension of the following primary communications messages:

- Tell your child's doctor when he/she starts using this medication
- This medication may temporarily slow the rate of growth in some children.

Both of these statements appear on the Warnings section of the proposed DFL in the section headed "*When using this product in children 2 to under 12 years of age*"

Additionally, the statement "*Tell your child's doctor when he/she starts using this medication*" also appears twice in the Directions section of the proposed DFL, in the section headed "children 6 to under 12 years of age and in the section headed "children 2 to under 6 years of age."

#### **C. Methodology**

The study took place from September 19 - September 27, 2012 in Los Angeles, Denver, Houston, Dallas and Tacoma. Respondents ages 16+ were randomly recruited through mall intercepts; after screening, data were collected in one-on-one interviews. Three dimensional

color packages that simulated the outer box packaging were provided for participants to read; participants were then asked questions by the interviewer.

Prior to the fielding of the study, a target threshold of 80% was set for both primary communication objectives.

#### **D. Survey**

Below are the two key questions addressing the two primary communications objectives:

- Question 3: When using this product in children 2 to under 6 years of age, what does the package say you should do when a child starts using this medication? (n=320)
- Question 4: “When using this product what does the package say may happen to some children 2 to under 12 years of age?” (n=305)

#### **E. Key Findings**

- **Comprehension of “Tell your child’s doctor when he/she starts using this medication”: 96.6%** (95% CI=93.9%-98.3%)
  - Approximately 90% provided this as an initial response; the other approximately 7% provided this as a response to a follow up question.
  - Responses for normal literacy and low literacy were the same.
- **Comprehension of “This medication may temporarily slow the rate of growth in some children”: 78.7%** (95% CI=73.7%-83.1%)
  - Responses for normal literacy and low literacy were significantly different.
    - Normal literacy 85%; low literacy 64%
    - Verbatims suggest that participants did not misunderstand the growth statement, but rather had difficulty finding it as it was not accorded the same label prominence as “tell your child’s doctor.” (Samples of verbatims are included below in Table 1)

**Table 1: Sample of Verbatims**

“I was looking at the dosing side of the package. I should have looked for it on the back side as well. I think it should be under the dosing instructions.”
“I was reading it from the side of the label. I didn’t think to check the back because I thought it would be in the area of dosing directions.”
“Most products have the thing on the side and that’s usually where I look for the important information, so I guess I just looked at the side instead of the back.”
“I was looking at the side of the package. The directions and use for kids should be together and not separated.”
“I think because you wouldn’t think that a nasal spray would stunt their growth and when I look at it, I just look at the dosages instead of looking at the rest of the box.”
“That probably should be bolded if it’s that important.”
“I think that’s an important sentence that needs to be in bold or at least highlighted, because I could not find it.”

## **F. Sponsor Conclusions**

The Sponsor asserts that of the two primary communication objectives, the more important message is to tell the child’s doctor at the start of using the medication, and that message was understood by nearly all the participants. While acknowledging that fewer correctly responded to the message about temporarily slowing in the rate of growth, the Sponsor states that the physician can provide counsel regarding the potential for growth effects if consumers follow the direction to inform the child’s doctor.

## **G. FDA Comments**

### **Methodology:**

This was not a nationally representative study; it targeted the South and West only. It’s possible that allergy sufferers/medication patterns might be different in various areas of the United States and therefore the data could be biased in either direction.

Moreover, scenario questions were not used and the question wording repeatedly cued the respondents to look at the package. The question wording also cued respondents to know that



something might happen to some children 2-12 years of age, rather than being more neutrally worded. Therefore the findings may be overstated.

### **Conclusions:**

It's unclear whether the "tell your child's doctor when he/she starts using this medication" statement is actually the more important of the two statements, since:

- "When" is vague in this context. It could be interpreted as the start day by one consumer and after several weeks or months by another, assuming it is not a forgotten follow-up altogether.
- In the OTC setting, consumers may or may not have a regular doctor. If a child does not have a regular pediatrician, the parent/caregiver might not think another doctor needs to be consulted, particularly since it doesn't have to happen *before* the child starts the medication.

Additionally:

- As the selected verbatims highlight, the "tell a doctor" sentence is in the directions section (twice) as well as in the warnings section. However, the growth statement is only in the warning section. Therefore, the "tell a doctor" naturally gets more visibility and thus comprehension.

### **Social Science Suggestions:**

- Replace the current sentence with "tell your child's doctor *before* he/she starts using this medication," to convey more of a sense of timeliness which in turn may prompt a greater likelihood of a consultation.
- Place the growth statement also in the directions section, as there would then be more likelihood that parents/caregivers would see it and understand why a doctor needs to be consulted.

## ***LCS of Drug Facts Label and Consumer Package Insert (#2012002)***

### **A. Background and Objectives:**

At June 2012 and November 2011 meetings with the Sponsor, FDA indicated that the label comprehension study could focus on the unique aspects of Nasacort as an OTC product. The Agency noted that the importance of preparing the pump (priming) before first use should be a primary communication objective for both the DFL and consumer package insert (CPI).

## **B. Methodology:**

This study had two phases and was conducted from July 16 – September 6, 2012. Only communications objectives that did not test well in Phase I were retested in Phase II. Standard mall intercept recruitment was utilized. Eligible respondents received either the DFL or CPI to read, and were then interviewed in one on one sessions. Research sites included Atlanta, Denver, Los Angeles, Minneapolis, Philadelphia, San Antonio, San Diego, Seattle, Tucson, Charlotte, Dallas and Louisville. In addition to the primary communications objective, the study had numerous secondary and informational objectives, which are listed along with results.

## **C. Key Findings: Summary of DFL Primary Communication Objective Results**

<b>Text from the Drug Facts Label</b>	<b>Overall Score (95% CI) Sample Size</b>	<b>Normal Literacy (95% CI) Sample Size</b>	<b>Low Literacy (95% CI) Sample Size</b>
Get a new bottle of Nasacort ready (primed) before first use	86.8% (82.6%-90.3%) N=325	93.3% (89.2%-96.2%) N=225	72% (62.1%-80.5%) N=100

## **D. Key Findings: Summary of CPI Primary Communication Objective Results**

<b>Text from the Consumer Package Insert</b>	<b>Overall Score (95% CI) Sample Size</b>	<b>Normal Literacy (95% CI) Sample Size</b>	<b>Low Literacy (95% CI) Sample Size</b>
Before first use, a new bottle must be primed.	88.6% (85.1%-91.5%) N=411	94.3% (91%-96.7%) N=283	75.8% (67.4%-82.9%) N=128

#### E. Summary of DFL Secondary Communication Objectives Results (#2012002)

<b>Text from the Drug Facts Label</b>	<b>Overall Score (95% CI) Sample Size*</b>	<b>Normal Literacy (95% CI) Sample Size</b>	<b>Low Literacy (95% CI) Sample Size</b>
Ask a doctor before use if you have had recent nasal ulcers, nasal surgery or nasal injury that have not healed	87.1% (82.9%-90.5%) N=325	89.3% (84.5%-93.0%) N=225	82.0% (73.1%-89.0%) N=100
Ask a doctor before use if you are using an asthma medicine or a prescription steroid medicine	88.6% (85.4%-91.3%) N=475	92.1% (88.6%-94.8%) N=329	80.8% (73.5%-86.9%) N=146
Ask a doctor before use if you have or had glaucoma or cataracts	88.2% (85.0%-91.0%) N=475	91.8% (88.3%-94.5%) N=329	80.1% (72.7%-86.3%) N=146
Stop use and ask a doctor if you have an allergic reaction, such as a rash, problems swallowing or breathing, swelling of your lips, face or tongue. Seek medical help right away.	97.7% (95.9%-98.8%) N=475	99.4% (97.8%-99.9%) N=329	93.8% (88.6%-97.1%) N=146

\* Sample sizes were different depending on whether testing for the specific objective was finalized in Phase 1 or Phase 2. Phase 1 sample was N=475; Phase 2 sample was N=325.

**F: Summary of DFL Other Communication Messages Results (#2012002)**

<b>Text from the Drug Facts Label</b>	<b>Overall Score (95% CI) Sample Size</b>	<b>Normal Literacy (95% CI) Sample Size</b>	<b>Low Literacy (95% CI) Sample Size</b>
Temporarily relieves these symptoms of hay fever or other respiratory allergies: nasal congestion, sneezing, runny nose, itchy nose	98.5% (97.0%- 99.4%) N=475	99.4% (97.8%-99.9%) N=329	97.3% (93.1%-99.2%) N=146
For ages 12 and older	98.7% (97.3%-99.5%) N=475	99.4% (97.8%-99.9%) N=329	97.3% (93.1%-99.2%) N=146
Frequency of dosing, age 12+	92.2% (89.4%-94.4%) N=475	93.9% (90.7%-96.2%) N=329	88.4% (82%-93.1%) N=146
Dosing for ages 6-under 12	98.7% (97.3%-99.5%) N=475	99.7% (98.3%-100%) N=329	96.6% (92.2%-98.9%) N=146
Dosing for ages 2 to under 6	96.2% (94.1%-97.7%) N=473	97.0% (94.5%-98.5%) N=328	94.5% (89.4%-97.6%) N=145
Frequency of dosing for ages 2 to under 6	95.3% (93.0%-97.1%) N=472	96.9% (94.4%-98.5%) N=327	91.7% (86.0%-95.7%) N=145
May reduce dose if symptoms improve	92.8% (90.1%-95.0%) N=475	93.6% (90.4%-96.0) N=329	91.1% (85.3%-95.2%) N=146
Action if symptoms do not improve within one week.	87.6% (84.3%-90.4%) N=475	89.1% (85.2%-92.2%) N=329	84.2% (77.3%-89.7%) N=146
Ask a health professional before use if breastfeeding	88.6% (85.2%-91.3%) N=475	91.2% (87.6%-94.0%) N=329	82.9% (75.8%-88.6%) N=146
Do not use if under 2	91.2% (88.2%-93.6%)	92.7% (89.3%-95.3%)	87.7% (81.2%-92.5%)

<b>Text from the Drug Facts Label</b>	<b>Overall Score (95% CI) Sample Size</b>	<b>Normal Literacy (95% CI) Sample Size</b>	<b>Low Literacy (95% CI) Sample Size</b>
years of age	N=475	N=329	N=146
Time to get some symptom relief	95.1% (92.1%-97.2%) N=325	96.9% (93.7%-98.7%) N=225	91.0% (83.6%-95.8%) N=100
Time to get 24 hour symptom relief	83.0% (78.4%-86.9%) N=323	87.9% (82.9%-91.9%) N=223	72.0% (62.1%-80.5%) N=100
Do not use if you are allergic to any of the ingredients	87.7% (84.4%-90.5%) N=472	90.8% (87.2%-93.7%) N=327	80.7% (73.3%-86.8%) N=145
Read insert (inside package) on how to: get a new bottle ready (primed) before first use; prime bottle again if not used for more than 2 weeks; use the spray; clean the spray nozzle.	88.0% (84.0%-91.3%) N=325	91.6% (87.1%-94.8%) N=225	80% (70.8%-87.3%) N=100
Stop use and ask a doctor if you have, or come into contact with someone who has, chickenpox, measles, or tuberculosis	92.0% (89.2%-94.3%) N=475	95.4% (92.6%-97.4%) N=329	84.2% (77.3%-89.7%) N=146

\* Sample sizes were different depending on whether testing for the specific objective was finalized in Phase 1 or Phase 2. Phase 1 sample was N=475; Phase 2 sample was N=325.

**G: Summary of CPI Secondary Communication Objectives (#2012002)**

<b>Text from the Consumer Package Insert</b>	<b>Overall Score (95% CI) Sample Size*</b>	<b>Normal Literacy (95% CI) Sample Size</b>	<b>Low Literacy (95% CI) Sample Size</b>
If a bottle is not used for more than two weeks, prime bottle again.	89.5% (86.2%-92.3%) N=411	96.5% (93.6%-98.3%) N=283	74.2% (65.7%-81.5%) N=128
If the pump does not spray properly, the nozzle may be blocked. Clean the nozzle.	96.0% (93.2%-97.8%) N=323	98.2% (95.4%-99.5%) N=219	91.3% (84.2%-96.0%) N=104
If the pump does not spray properly: Never try to unblock the nozzle with a pin or any object.	95.7% (92.8%-97.6%) N=323	97.3% (94.1%-99.0%) N=219	92.3% (85.4%-96.6%) N=104

\* Sample sizes were different depending on whether testing for the specific objective was finalized in Phase 1 or Phase 2. Phase 1 sample was N=323 and Phase 2 was N=411.

## H: Summary of CPI Other Communication Messages Results

Text from the Consumer Package Insert	Overall Score (95% CI) Sample Size*	Normal Literacy (95% CI) Sample Size	Low Literacy (95% CI) Sample Size
If you get the spray in your eyes, rinse well with water.	95% (92% - 97.1%) N=321	95.4% (91.7%-97.8%) N=218	94.2% (87.8%-97.8%) N=103
Adults should supervise use in children	91.7% (88.6%-94.2%) N=411	95.8% (92.7%-97.8%) N=283	82.8% (75.1%-88.9%) N=128
If you forget a dose, use only as directed. DO NOT DOUBLE DOSE	87.3% (83.7%-90.4%) N=410	91.5% (87.6%-94.5%) N=283	78.0% (69.7%-84.8%) N=127
Aim nozzle toward back of nose. Do NOT spray toward nasal septum (the wall between the 2 nostrils)	94.6% (92.0%-96.6%) N=411	97.2% (94.5%-98.8%) N=283	89.1% (82.3%-93.9%) N=128

\* Sample sizes were different depending on whether testing for the specific objective was finalized in Phase 1 or Phase 2. Phase 1 sample was N=323 and Phase 2 was N=411.

### Sponsor Conclusions:

The Sponsor concludes that the comprehension of the primary communications objectives was acceptable.

### FDA Comments:

The Sponsor did not use scenarios in the wording of many of the questions (See Appendix, p.67). Moreover, the wording of some of the questions cued that an action was to be taken as contrasted with more neutral wording. Therefore, it is possible that some of the findings are overstated.

Additionally, although some of the lower scoring findings (particularly among low literacy respondents) do not pose significant safety issues on their own, when examined within the potential implications of the growth study, they may be less than optimal. Examples are:

- Do not use under two years of age

- Do not double dose
- Children should be supervised when taking the medication

Depending on what the magnitude of adverse growth effects would be if these directions are not adhered to, the Sponsor may wish to consider making these statements more prominent.

## ***Usability/Human Factors Study (#2012026)***

### **A. Objectives**

This study assessed the ability of adult users, children and caregivers to correctly execute the following functions:

1. Getting a new bottle ready for first use
2. Cleaning the product if the pump does not spray properly
3. Getting a used bottle ready if it has not been used for two weeks or more.(i.e., re-priming)

### **B. Methodology**

This study took place in Bala Cynwyd, PA on September 19-30, 2012. In each one-on-one session, the moderator asked the participant to imagine that he/she had recently purchased Nasacort and was opening it for the first time. (The bottles were filled with placebo liquid and the tasks did not include administration of the product.) The moderator then showed the participant the consumer package insert and asked that the participant read the instructions. The moderator then introduced each task with a specific scenario and recorded the participant's actions. Each participant was asked to handle the product, to behave as they would in each actual scenario, and to describe what he/she would do.

**User 1 Group** – Caregivers (of children between 2 and 12 years old who suffer from nasal symptoms of seasonal and perennial allergic rhinitis) n=20, mix of gender, age and literacy levels.

**User 2 Group** – Sufferers of nasal symptoms of seasonal and perennial allergic rhinitis, between the ages of 12 and 21, n=17, mix of gender, age and literacy levels. Some were supervised by their respective caregivers.

**User 3 Group** – Adult sufferers, at least 21 years of age, of nasal symptoms of seasonal and perennial allergic rhinitis, n=16, mix of gender, age and literacy levels.

### **C. Key Findings:**



Note: There was no meaningful difference in the performance of participants between Groups 1, 2, and 3; therefore, data from all three groups are presented together. Moreover, although there were only 10 naïve users and so it is difficult to extrapolate the findings, it appears that there were no meaningful differences in the performance of participants who were naïve users (had never used a nasal spray pump before) versus those who had used one previously.

### **Preparing Pump for First Use:**

- All participants recognized that there were unique instructions for preparing the nasal spray for first use.
- All participants successfully removed the cap.
- Almost all participants (91%) shook the product.
- Most participants (82%) successfully pressed and released the spray nozzle until a fine mist was produced.
- Overall 75% of participants identified the need to prepare a new bottle and correctly completed all of the steps listed on the CPI to prepare the product for first use.

### **Maintenance:**

- Most (87%) of participants recognized that preparation was necessary for use after two weeks of non-use.
- Almost all (96%) of the participants removed the cap; all who tried were successful.
- Most (79%) correctly shook the product.
- Most (85%) correctly pressed and released the spray nozzle until a fine spray was produced.
- Overall, 68% of participants identified the need to re-prime the bottle after two weeks of non-use and correctly completed all of the steps listed on the CPI to prepare a product for re-use.

### **Cleaning:**

- Almost all participants (94%) correctly recognized that they should attempt to clean the spray nozzle to fix a clog.
- Almost all participants (92%) successfully pulled the spray nozzle away from the bottle.
- Most of the participants rinsed (80%) the nozzle correctly.
- Almost all participants (90%) correctly shook or tapped to remove excess water.
- Almost all participants (91%) successfully reattached the spray nozzle to the bottle.
- Most participants (83%) successfully pressed and released the spray nozzle until a fine spray was produced after cleaning.

- Overall, 73% of participants identified the need to clean the nozzle to clear a clog and correctly demonstrated all the steps listed on the CPI for cleaning the spray nozzle.

### **Sponsor Conclusions:**

The Sponsor concludes that failure to perform any of the steps discussed above has a very low safety risk, but may have an impact on efficacy due to not receiving a full dose or missing a dose. While a missed dose or doses could result in nasal symptoms returning, Nasacort does not involve any withdrawal concerns and thus there are no safety risks in this regard. Furthermore, impact on efficacy would be minimal. In the case of failing to prime/re-prime the pump, this would be self-corrected by a subsequent actuation when administering a follow up dose. In the case of failing to clean a clogged nozzle, if nothing is being dispensed most likely the instructions would be re-read, or the bottle not used.

The Sponsor concludes that since most failures were a consequence of not reading the instructions or forgetting to do a step, no modifications to the CPI are necessary.

### **FDA Comments:**

Regarding priming of the bottle, four participants attempted to prime the bottle but prematurely stopped when they mistakenly misinterpreted the initial discharge as the referenced “fine mist. Regarding repriming of the bottle, seven participants did not recognize that preparation was also necessary for use after two weeks of non-use.

### **Social Science Suggestions:**

The Sponsor may wish to consider adding a sentence to Section 2 of the CPI to the effect that users may need to press and release several times before the mist is produced.

The need to re-prime the bottle after two weeks of non-use should also be emphasized more; although it is bolded, it is still in the section headed “Steps to Get a New Bottle Ready for Use”. The Sponsor may want to consider putting this in a separate section.

## **Appendix - Questions in Label Comprehension Study of Drug Facts Label and Consumer Package Insert (#2012002)**

### **Drug Facts Label – Phase 1:**

1. What is Nasacort used for?
2. According to the package, how many sprays per nostril per day should a person 12 years of age and older use?
3. How many times per day should a person 12 years of age and older use 2 sprays per nostril?
4. John is 9 years old. How many sprays per nostril should he use per day?
5. Laura has been using Nasacort for a week and she doesn't feel like her symptoms have improved. What if anything should she do?
6. Janelle is breast feeding her baby and wants to use this product. What does the label say about this?
7. Tim is 44 years old. After using Nasacort for a couple of weeks, his allergy symptoms are now improved. He continues to use the product to control his allergy symptoms. According to the label, how many sprays per nostril per day may he now use?
8. George has had nasal surgery that has not yet healed. He wants to use Nasacort to treat his hay fever symptoms. What if anything does the label say about this?
9. What if anything does that label say a person using this product should do if she comes into contact with someone who has the measles?
10. Joan uses an asthma medication to treat her asthma. She also has hay fever and is thinking about using Nasacort to treat her hay fever symptoms. What if anything does the label say Joan should do?
11. Julie has a daughter who is one year old. The daughter has upper respiratory allergies and her mother is thinking about buying the medicine for her to use. Is it ok or not ok for the daughter to use this product?
12. Bill used the product last night and wakes up with a rash on his chest. What if anything does the label say about this?
13. Robert has glaucoma. He would like to use this product to treat his hay fever. What instructions does the label give Robert?
14. What does the label say must be done to the pump before first use?
15. Where are the complete directions for preparing the pump for use, using the spray and cleaning the spray nozzle?
16. What does the label say about using Nasacort if you are allergic to any of the ingredients?
17. What is the shortest amount of time a person using this product can expect to get symptom improvement?
18. Jill is using this product and received some relief after using it for two days. How long might it take Jill to get 24 hour symptom relief with this product?
19. Lucy is 4 years old. How many sprays per nostril should she be given daily?
20. How many times per day should Lucy be given one spray per nostril?

### **Drug Facts Label - Phase 2**

1. A person has recently had nasal surgery that has not healed. What does the package say he should do if he wants to use Nasacort to treat his hay fever symptoms?
2. According to what you just read, is there an insert inside the package?
3. What does the package say should be done to a new bottle of Nasacort before first use?
4. When using this product, when can someone expect to get some symptom relief?
5. If you use this product daily, how long may it take you to get 24 hour symptom relief?

### **Consumer Package Insert - Phase 1**

1. According to the package insert, what should you do if you get this medicine in your eyes?
2. What does the label say must be done to the pump before first use?
3. Mary has not used Nasacort for three months. She has allergy symptoms again. What if anything do the instructions on the package insert say to do to the Nasacort pump before she uses it again?
4. Jim uses Nasacort every morning. One morning Jim wakes up and realizes he forgot to take Nasacort the previous morning. What does the package insert say about this?
5. If the pump does not spray properly, what do the instructions say you should do?
6. If the pump does not spray properly, what do the instructions say you should not do to unblock the nozzle?
7. I would like you to pretend that you are instructing me about how to use Nasacort. Tell me how I should position the spray nozzle in my nostril/
8. Paul is five years old. The directions say he can use one spray per nostril per day. What other directions are there for giving Nasacort to someone who is around Paul's age?

### **Consumer Package Insert - Phase 2**

1. According to what you just read, what must you do to a new bottle of Nasacort before first use?
2. What should you do to a bottle of Nasacort that has not been used for more than two weeks?
3. Jim uses Nasacort every morning. One morning Jim realizes he forgot to take a dose of Nasacort the previous morning. What does the insert say about this?
4. When a person uses this product, tell me how he should aim the nozzle.
5. Is it ok or not ok for a child to use this unsupervised?

# Appendix 1 – Proposed Drug Facts Labeling

## Tradename

### Drug Facts

Active ingredient (in each spray)	Purpose
Triamcinolone acetonide 55 mcg . . . . .	Nasal allergy reliever

### Uses

temporarily relieves these symptoms of hay fever or other upper respiratory allergies  
 ▪ nasal congestion ▪ runny nose ▪ sneezing ▪ itchy nose

### Warnings

#### Do not use

- if you are allergic to any of the ingredients

#### Ask a doctor before use if you

- have had recent nasal ulcers, nasal surgery or nasal injury that have not healed
- are using an asthma medicine or prescription steroid medicine
- currently have an eye infection
- have or had glaucoma or cataracts

#### When using this product

##### ▪ in children 2 to under 12 years of age:

- tell your child's doctor when he/she starts using this medication
- this medication may temporarily slow the rate of growth in some children
- symptom improvement can start within the first day of treatment
- it may take up to one week of daily use for 24-hour symptom relief
- do not share this bottle with anyone else as this may spread germs

#### Stop use and ask a doctor if

- you have an allergic reaction, such as a rash, problems swallowing or breathing, or swelling of your lips, face or tongue. Seek medical help right away
- you have, or come into contact with someone who has chickenpox, measles or tuberculosis
- you have or develop symptoms of an infection such as a persistent fever
- you have any change in vision
- you have severe or frequent nosebleeds

**If pregnant or breast-feeding**, ask a health professional before use.

**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

### Directions

Read insert (inside package) on how to:

- get a new bottle ready (primed) before first use
- prime bottle again if not used for more than 2 weeks
- use the spray
- clean the spray nozzle

adults and children 12 years of age and older	<ul style="list-style-type: none"> <li>▪ once daily, spray 2 times into each nostril</li> <li>▪ once your allergy symptoms improve, reduce to 1 spray in each nostril per day</li> </ul>
children 6 to under 12 years of age	<ul style="list-style-type: none"> <li>▪ when starting use, tell your child's doctor</li> <li>▪ once daily, spray 1 time into each nostril</li> <li>▪ if allergy symptoms do not improve, increase to 2 sprays in each nostril per day</li> <li>▪ once allergy symptoms improve, reduce to 1 spray in each nostril per day</li> <li>▪ an adult should supervise use</li> </ul>
children 2 to under 6 years of age	<ul style="list-style-type: none"> <li>▪ when starting use, tell your child's doctor</li> </ul>

	<ul style="list-style-type: none"> <li>▪ once daily, spray 1 time into each nostril</li> <li>▪ an adult should supervise use</li> </ul>
<b>children under 2 years of age</b>	<ul style="list-style-type: none"> <li>▪ do not use</li> </ul>

- do not use more than directed
- shake well before each use
- do not spray into eyes or mouth
- if allergy symptoms do not improve after one week, stop using and talk to a doctor

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#### ***Other information***

- **do not use if sealed package is torn or opened**
- keep package and insert. They contain important information.
- store between 20° to 25° C (68° to 77°F)

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#### ***Inactive ingredients***

benzalkonium chloride, carboxymethylcellulose sodium, dextrose, edetate disodium, hydrochloric acid or sodium hydroxide (for pH adjustment), microcrystalline cellulose, polysorbate 80

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#### ***Questions or comments?***

call toll-free **1-800-XXX-XXXX** or visit [www.Tradename.com](http://www.Tradename.com)

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## **Appendix 2 – Current Prescription Labeling**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NASACORT AQ safely and effectively. See full prescribing information for NASACORT AQ.

**Nasacort® AQ (triamcinolone acetonide) Nasal Spray**  
**Initial U.S. Approval: 1957**

### -----INDICATIONS AND USAGE-----

- NASACORT AQ Nasal Spray is a corticosteroid indicated for treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older. (1)

### -----DOSAGE AND ADMINISTRATION-----

- Adults and adolescents ≥ 12 years* Starting and maximum dose is 220 mcg/day (two sprays in each nostril once daily). (2.1)
- Children 6 to 12 years of age* Starting dose is 110 mcg/day (one spray in each nostril once daily). Maximum dose is 220 mcg/day (two sprays per nostril once daily). (2.2)
- Children 2 to 5 years of age* Starting and maximum dose 110 mcg/day (one spray in each nostril once daily). (2.2)
- Priming/Use:* For intranasal use only. Shake well before each use. Before using for the first time, release 5 sprays into the air away from the face. If the product is not used for more than 2 weeks, release 1 spray into the air before using. (2.3)

### -----DOSAGE FORMS AND STRENGTHS-----

- Nasal Spray: 55 mcg triamcinolone acetonide in each spray. (3)

### -----CONTRAINDICATIONS-----

- Do not administer to patients with history of hypersensitivity to triamcinolone acetonide or any ingredients of this product. (4)

### -----WARNINGS AND PRECAUTIONS-----

- Epistaxis, nasal septal perforation, *Candida albicans* infection, impaired wound healing. Monitor patients periodically for signs of adverse effects

on the nasal mucosa. Avoid use in patients with recent nasal septal ulcers, nasal surgery, or trauma. (5.1)

- Development of glaucoma or posterior subcapsular cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. (5.2)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patient with the above because of the potential for worsening of these infections. (5.3)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue NASACORT AQ Nasal Spray slowly. (5.4)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving NASACORT AQ Nasal Spray. (5.5, 8.4)

### -----ADVERSE REACTIONS-----

- Most common adverse reactions (>2% incidence) were pharyngitis, epistaxis, flu syndrome, cough increased, bronchitis, dyspepsia, tooth disorder, headache, pharyngolaryngeal pain, nasopharyngitis, abdominal upper pain, diarrhea, and excoriation. (6.1)
- Other adverse reactions, including serious adverse reactions, have been reported. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### -----USE IN SPECIFIC POPULATIONS-----

NASACORT AQ should be used during pregnancy only if potential benefit justifies potential risk to fetus. (8.1)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 07/2013**

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- 2.2 Children 2 to 12 Years of Age
- 2.3 Administration Information

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\*Sections or subsections omitted from the full prescribing information are not listed.



## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

NASACORT AQ Nasal Spray is indicated for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 2 years of age and older.

### **2 DOSAGE AND ADMINISTRATION**

Administer NASACORT AQ Nasal Spray by the intranasal route only. Shake NASACORT AQ Nasal Spray well before each use.

#### **2.1 Adults and Adolescents 12 Years of Age and Older**

The recommended starting and maximum dose is 220 mcg per day as two sprays in each nostril once daily. Titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose to 110 mcg per day (one spray in each nostril once a day) has been shown to be effective in maintaining control of the allergic rhinitis symptoms.

#### **2.2 Children 2 to 12 Years of Age**

*Children 6 to 12 years of age:* The recommended starting dose is 110 mcg per day given as one spray in each nostril once daily. Children not responding adequately to 110 mcg per day may use 220 mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 110 mcg once daily [see *Warnings and Precautions* (5.5), *Use in Specific Populations* (8.4) and *Clinical Pharmacology* (12.2)].

*Children 2 to 5 years of age:* The recommended and maximum dose is 110 mcg per day given as one spray in each nostril once daily [see *Warnings and Precautions* (5.5), *Use in Specific Populations* (8.4) and *Clinical Pharmacology* (12.2)].

NASACORT AQ Nasal Spray is not recommended for children under 2 years of age.

#### **2.3 Administration Information**

Priming: Prime NASACORT AQ Nasal Spray before using for the first time by shaking the contents well and releasing 5 sprays into the air away from the face. It will remain adequately primed for two weeks. If the product is not used for more than 2 weeks, then it can be adequately reprimed with one spray. Shake NASACORT AQ Nasal Spray well before each use.

If adequate relief of symptoms has not been obtained after 3 weeks of treatment, NASACORT AQ Nasal Spray should be discontinued [see *Warnings and Precautions* (5), *Patient Counseling Information* (17), and *Adverse Reactions* (6)].

### **3 DOSAGE FORMS AND STRENGTHS**

NASACORT AQ Nasal Spray is a metered-dose pump spray containing the active ingredient triamcinolone acetonide. Each actuation delivers 55 mcg triamcinolone acetonide from the nasal actuator after an initial priming of 5 sprays. Each 16.5 gram bottle (120 actuations) contains 9.075 mg of triamcinolone acetonide. The bottle should be discarded when the labeled-number of actuations have been reached even though the bottle is not completely empty.

## 4 CONTRAINDICATIONS

NASACORT AQ should not be administered to patients with a history of hypersensitivity to triamcinolone acetonide or to any of the other ingredients of this preparation.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Local Nasal Effects

**Epistaxis:** In clinical studies of 2 to 12 weeks duration, epistaxis was observed more frequently in patients treated with NASACORT AQ Nasal Spray than those who received placebo [*see Adverse Reactions (6)*].

**Nasal Septal Perforation:** In clinical trials, nasal septum perforation was reported in one adult patient treated with NASACORT AQ Nasal Spray.

**Candida Infection:** In clinical studies with NASACORT AQ Nasal Spray, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local or systemic therapy and discontinuation of NASACORT AQ Nasal Spray. Therefore, patients using NASACORT AQ Nasal Spray over several months or longer should be examined periodically for evidence of Candida infection or other signs of adverse effects on the nasal mucosa.

**Impaired Wound Healing:** Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, surgery, or trauma should not use NASACORT AQ Nasal Spray until healing has occurred.

### 5.2 Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts.

### 5.3 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or have not been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections, or ocular herpes simplex because of the potential for worsening of these infections.

## 5.4 Hypothalamic-Pituitary-Adrenal Axis Effects

**Hypercorticism and Adrenal Suppression:** When intranasal steroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of NASACORT AQ Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms.

## 5.5 Effect on Growth

Corticosteroids, including NASACORT AQ Nasal Spray, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving NASACORT AQ Nasal Spray. To minimize the systemic effects of intranasal corticosteroids, including NASACORT AQ Nasal Spray, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [*see Use in Specific Populations (8.4)*].

## 6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Epistaxis, *Candida albicans* infection, nasal septal perforation, impaired wound healing [*see Warnings and Precautions (5.1)*]
- Glaucoma and Cataracts [*see Warnings and Precautions (5.2)*]
- Immunosuppression [*see Warnings and Precautions (5.3)*]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see Warnings and Precautions (5.4, 5.5), Use in Specific Populations (8.4) and Clinical Pharmacology (12.2)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In placebo-controlled, double-blind, and open-label clinical studies, 1483 adults and children 12 years and older received treatment with NASACORT AQ Nasal Spray. These patients were treated for an average duration of 51 days. In the controlled trials (2-5 weeks duration) from which the following adverse reaction data are derived, 1394 patients were treated with NASACORT AQ Nasal Spray for an average of 19 days. In a long-term, open-label study, 172 patients received treatment for an average duration of 286 days. Adverse reactions from 12 studies in adults and adolescent patients 12 to 17 years of age receiving NASACORT AQ Nasal Spray 27.5 mcg to 440 mcg once daily are summarized in Table 1.

In clinical trials, nasal septum perforation was reported in one adult patient who received NASACORT AQ Nasal Spray.

**Table 1 - Adverse drug reactions > 2% and greater than placebo with NASACORT AQ Nasal Spray 220 mcg treatment in studies in adults and adolescents 12 years and older**

	Placebo (N=962)	NASACORT AQ 220 mcg (N=857)
Adverse reaction	%	%
Pharyngitis	3.6	5.1
Epistaxis	0.8	2.7
Cough increased	1.5	2.1

Coding dictionary for adverse events is Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).

A total of 602 children 6 to 12 years of age were studied in 3 double-blind, placebo-controlled clinical trials. Of these, 172 received 110 mcg/day and 207 received 220 mcg/day of NASACORT AQ Nasal Spray for two, six, or twelve weeks. The longest average durations of treatment for patients receiving 110 mcg/day and 220 mcg/day were 76 days and 80 days, respectively. One percent of patients treated with NASACORT AQ were discontinued due to adverse experiences. No patient receiving 110 mcg/day and one patient receiving 220mcg/day discontinued due to a serious adverse event. A similar adverse reaction profile was observed in pediatric patients 6-12 years of age as compared to adolescents and adults with the exception of epistaxis which occurred in less than 2% of the children studied. Adverse reactions from 2 studies in children 4 to 12 years of age receiving NASACORT AQ Nasal Spray 110 mcg once daily are summarized in Table 2.

**Table 2 - Adverse drug reactions > 2% and greater than placebo with NASACORT AQ Nasal Spray 110 mcg treatment in US studies in patients 4 to 12 years of age**

	Placebo (N=202)	NASACORT AQ 110 mcg (N=179)
Adverse reaction	%	%
Flu syndrome	7.4	8.9
Cough increased	6.4	8.4
Pharyngitis	6.4	7.8
Bronchitis	1.0	3.4
Dyspepsia	1.0	3.4
Tooth disorder	1.0	3.4

Coding dictionary for adverse events is Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART).

A total of 474 children 2 to 5 years of age were studied in a 4-week double-blind, placebo-controlled clinical trial. Of these, 236 received 110 mcg/day of NASACORT AQ Nasal Spray for a mean duration of 28 days. No patient discontinued due to a serious adverse event. Adverse

reactions from the single placebo-controlled study in children 2 to 5 years of age receiving NASACORT AQ Nasal Spray 110 mcg once daily are summarized in Table 3.

**Table 3 - Adverse drug reactions > 2% and greater than placebo with NASACORT AQ Nasal Spray 110 mcg treatment in children 2 to 5 years of age**

Adverse reactions	Placebo (N=238)	NASACORT AQ 110 mcg (N=236)
	%	%
Headache	4.2	5.5
Pharyngolaryngeal pain	4.2	5.5
Epistaxis	5.0	5.1
Nasopharyngitis	3.8	5.1
Abdominal upper pain	0.8	4.7
Diarrhea	1.3	3.0
Asthma	2.1	2.5
Rash	1.7	2.5
Excoriation	0.0	2.5
Rhinorrhea	1.7	2.1

Coding dictionary for adverse events is Medical Dictionary for Regulatory Activities terminology (MedDRA) Version 8.1

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but acute systemic adverse experiences are unlikely [see *Overdosage (10)*].

## 6.2 Post-Marketing Experience

In addition to the adverse drug reactions reported during clinical studies and listed above, the following adverse reactions have been identified during post-approval use of NASACORT AQ Nasal Spray. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reactions that have been reported during post-marketing experience include: nasal discomfort and congestion, sneezing, alterations of taste and smell, nausea, insomnia, dizziness, fatigue, dyspnea, decreased blood cortisol, cataract, glaucoma, increased ocular pressure, pruritus, rash, and hypersensitivity.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of NASACORT AQ Nasal Spray in pregnant women. Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. NASACORT AQ Nasal Spray, like other corticosteroids, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Since their introduction, experience with oral corticosteroids in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a

natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

In reproduction studies in rats and rabbits, triamcinolone acetonide administered by inhalation produced cleft palate and/or internal hydrocephaly and axial skeletal defects at exposures less than and 2 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis. In a monkey reproduction study, triamcinolone acetonide administered by inhalation produced cranial malformations at an exposure approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis.

### **8.3 Nursing Mothers**

It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when NASACORT AQ Nasal Spray is administered to nursing women.

### **8.4 Pediatric Use**

The safety and effectiveness of NASACORT AQ Nasal Spray has been evaluated in 464 children 2 to 5 years of age, 518 children 6 to 12 years of age, and 176 adolescents 12 to 17 years of age [see *Clinical Studies* (14)]. The safety and effectiveness of NASACORT AQ Nasal Spray in children below 2 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height are unknown. The potential for “catch-up” growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including NASACORT AQ Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including NASACORT AQ Nasal Spray, each patient’s dose should be titrated to the lowest dosage that effectively controls his/her symptoms.

The effect of NASACORT AQ Nasal Spray on growth velocity in children was assessed in a 12 month randomized, placebo controlled study conducted in 299 prepubescent children age 3 to 9 years (173 males, 126 females) with perennial allergic rhinitis. Treatment groups were NASACORT AQ 110 mcg once daily and placebo. Growth velocity was estimated for each patient using the slope of the linear regression of height over time using observed data in the intent to treat population who had at least 3 height measurements after randomization. Growth velocities were significantly lower in the NASACORT AQ group compared to placebo, with a mean growth velocity of 6.09 cm/year in the placebo group and 5.65 cm/year in the NASACORT AQ treated group (difference from placebo -0.45 cm/year; 95% CI: -0.78, -0.11).

## 8.5 Geriatric Use

Clinical studies of NASACORT AQ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

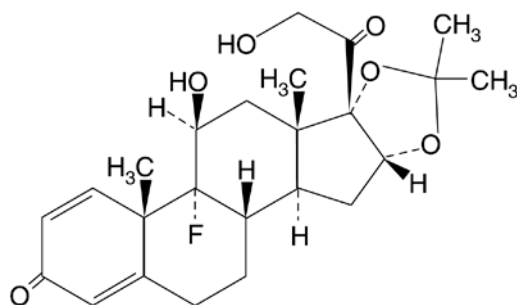
## 10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism [see *Warnings and Precautions* (5.4)]. There are no data on the effects of acute or chronic overdosage with NASACORT AQ Nasal Spray. Because of low systemic bioavailability and an absence of acute drug-related systemic findings in clinical studies overdose is unlikely to require any therapy other than observation.

Acute overdosing with the intranasal dosage form is unlikely in view of the total amount of active ingredient present and low bioavailability of triamcinolone acetonide. In the event that the entire contents of the bottle were administered all at once, via either oral or nasal application, clinically significant systemic adverse events would most likely not result.

## 11 DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in NASACORT AQ Nasal Spray, is a corticosteroid with a molecular weight of 434.51 and with the chemical designation 9-Fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone (C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>).



NASACORT AQ Nasal Spray is a thixotropic, water-based metered-dose pump spray formulation unit containing a microcrystalline suspension of triamcinolone acetonide in an aqueous medium. Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, dextrose, benzalkonium chloride, and edetate disodium are contained in this aqueous medium; hydrochloric acid or sodium hydroxide may be added to adjust the pH to a target of 5.0 within a range of 4.5 and 6.0.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Triamcinolone acetonide is a synthetic fluorinated corticosteroid with approximately 8 times the potency of prednisone in animal models of inflammation.

Although the precise mechanism of corticosteroid antiallergic action is unknown, corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

## 12.2 Pharmacodynamics

In order to determine if systemic absorption plays a role in the effect of NASACORT AQ Nasal Spray on allergic rhinitis symptoms, a two week double-blind, placebo-controlled clinical study was conducted comparing NASACORT AQ, orally ingested triamcinolone acetonide, and placebo in 297 adult patients with seasonal allergic rhinitis. The study demonstrated that the therapeutic efficacy of NASACORT AQ Nasal Spray can be attributed to the topical effects of triamcinolone acetonide.

**Adrenal Function:** In order to evaluate the effects of systemic absorption on the Hypothalamic-Pituitary-Adrenal (HPA) axis, 4 clinical studies, one each in adults and in children 6-12 years of age, 2-5 years of age, and 2-11 years of age, were conducted.

The adult clinical study compared 220 mcg or 440 mcg NASACORT AQ per day, or 10 mg prednisone per day with placebo for 42 days. Adrenal response to a six-hour 250 mcg cosyntropin stimulation test showed that NASACORT AQ administered at doses of 220 mcg and 440 mcg had no statistically significant effect on HPA activity versus placebo. Conversely, oral prednisone at 10 mg/day significantly reduced the response to ACTH.

A study evaluating plasma cortisol response thirty and sixty minutes after 250 mcg cosyntropin stimulation in 80 pediatric patients 6 to 12 years of age who received 220 mcg or 440 mcg (twice the maximum recommended daily dose) daily for six weeks was conducted. No abnormal response to cosyntropin infusion (peak serum cortisol <18 mcg/dL) was observed in any pediatric patient after six weeks of dosing with NASACORT AQ at 440 mcg per day.

In pediatric patients 2 to 5 years of age (n = 61) receiving Nasacort AQ 110 mcg per day intranasally, HPA axis function was assessed by cosyntropin stimulation test; however, the results were inconclusive.

An effect of Nasacort AQ Nasal Spray on adrenal function in children 2 to 5 years of age cannot be ruled out.

In a 6-week trial in 140 children 2 to 11 years of age with allergic rhinitis, a daily dose of 110 or 220 mcg of NASACORT AQ Nasal Spray was compared to placebo nasal spray. A subset of 24 children 6 to 11 years of age received a higher dose of 220 mcg of NASACORT AQ Nasal Spray. A positive control was not included in this trial. Adrenal function was assessed by measurement of 24 hour serum cortisol levels before and after the treatment. The difference from placebo in the change from baseline in LS mean serum cortisol AUC<sub>(0-24 hr)</sub> at the end of week 6 for the NASACORT AQ Nasal Spray treatment groups (110 mcg and 220 mcg) was -4.2 mcg•hour/dL (95% CI: -14.7, 6.4).



### 12.3 Pharmacokinetics

Based upon intravenous dosing of triamcinolone acetonide phosphate ester in adults, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.5 L (SD  $\pm$  27.5) and clearance was 45.2 L/hour (SD  $\pm$  9.1) for triamcinolone acetonide. The plasma half-life of corticosteroids does not correlate well with the biologic half-life.

Pharmacokinetic characterization of the NASACORT AQ Nasal Spray formulation was determined in both normal adult subjects and patients with allergic rhinitis. Single dose intranasal administration of 220 mcg of NASACORT AQ Nasal Spray in normal adult subjects and patients demonstrated minimal absorption of triamcinolone acetonide. The mean peak plasma concentration was approximately 0.5 ng/mL (range: 0.1 to 1.0 ng/mL) and occurred at 1.5 hours post dose. The mean plasma drug concentration was less than 0.06 ng/mL at 12 hours, and below the assay detection limit (the minimum LOQ of the assay was 0.025 ng/ml) at 24 hours. The average terminal half-life was 3.1 hours. The range of mean AUC<sub>0-∞</sub> values was 1.4 ng•hr/mL to 4.7 ng•hr/mL between doses of 110 mcg to 440 mcg in both patients and healthy volunteers. Dose proportionality was demonstrated in both normal adult subjects and in allergic rhinitis patients following single intranasal doses of 110 mcg or 220 mcg NASACORT AQ Nasal Spray. The C<sub>max</sub> and AUC<sub>0-∞</sub> of the 440 mcg dose increased less than proportionally when compared to 110 and 220 mcg doses.

Following multiple dose administration of NASACORT AQ 440 mcg once daily in pediatric patients 6 to 12 years of age, plasma drug concentrations, AUC<sub>0-∞</sub>, C<sub>max</sub> and T<sub>max</sub> were similar to those values observed in adult patients receiving the same dose. Intranasal administration of NASACORT AQ 110 mcg once daily in pediatric patients 2 to 5 years of age exhibited similar systemic exposure to that achieved in adult patients 20 to 49 years of age with intranasal administration of NASACORT AQ at a dose of 220 mcg once daily. Based on the population pharmacokinetic modeling, the apparent clearance and volume of distribution following intranasal administration of NASACORT AQ in pediatric patients 2 to 5 years of age were found to be approximately half of that in adults.

In animal studies using rats and dogs, three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 1.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults and children on a mcg/m<sup>2</sup> basis, respectively). In a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 3.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults and children on a mcg/m<sup>2</sup> basis, respectively).

No evidence of mutagenicity was detected from *in vitro* tests (a reverse mutation test in *Salmonella* bacteria and a forward mutation test in Chinese hamster ovary cells) conducted with triamcinolone acetonide.

In male and female rats, triamcinolone acetonide caused no change in pregnancy rate at oral doses up to 15.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). Triamcinolone acetonide caused increased fetal resorptions and stillbirths and decreases in pup weight and survival at doses of 5.0 mcg/kg and above (less than the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). At 1.0 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis), it did not induce the above mentioned effects.

### 13.2 Animal Toxicology and/or Pharmacology

Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. In rats, triamcinolone acetonide was teratogenic at an inhalation dose of 20 mcg/kg and above (approximately 7/10 of the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). In rabbits, triamcinolone acetonide was teratogenic at inhalation doses of 20 mcg/kg and above (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). In monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 500 mcg/kg (approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). Dose-related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects, whereas the effects observed in the monkey were cranial malformations.

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

## 14 CLINICAL STUDIES

The safety and efficacy of NASACORT AQ Nasal Spray have been evaluated in 10 double-blind, placebo-controlled clinical studies of two- to four-weeks duration in adults and children 12 years and older with seasonal or perennial allergic rhinitis. The number of patients treated with NASACORT AQ Nasal Spray in these studies was 1266; of these patients, 675 were males and 591 were females.

Overall, the results of these clinical studies in adults and children 12 years and older demonstrated that NASACORT AQ Nasal Spray 220 mcg once daily (2 sprays in each nostril),

when compared to placebo, provides statistically significant relief of nasal symptoms of seasonal or perennial allergic rhinitis including sneezing, stuffiness, discharge, and itching.

The safety and efficacy of NASACORT AQ Nasal Spray, at doses of 110 mcg or 220 mcg once daily, have also been adequately studied in two double-blind, placebo-controlled studies of two- and twelve-weeks duration in children ages 6 through 12 years with seasonal and perennial allergic rhinitis. These studies included 341 males and 177 females. NASACORT AQ administered at either dose resulted in statistically significant reductions in the severity of nasal symptoms of allergic rhinitis.

The safety and efficacy of NASACORT AQ Nasal Spray in children 2 to 5 years of age with perennial allergic rhinitis with or without seasonal allergic rhinitis was studied in a single 4 week double blind, placebo controlled clinical study with a 24 week open label extension conducted in the United States. The study included 464 patients (266 males and 198 females) 2 to 5 years of age who received at least one dose of study medication (233 placebo, 231 NASACORT AQ 110 mcg once daily). Efficacy was determined over a four-week double-blind, placebo-controlled treatment period and was based on patient's parent or guardian recording of four nasal symptoms (total nasal symptom score, TNSS), congestion, itching, rhinorrhea, and sneezing on a 0-3 categorical severity scale (0=absent, 1=mild, 2=moderate, and 3=severe) once daily. Reflective scoring (rTNSS) required recording symptom severity over the previous 24 hours; the instantaneous scoring (iTNSS) required recording symptom severity at the time just prior to dosing. Baseline symptom severity was comparable between NASACORT AQ and placebo respectively, for iTNSS (7.52, 7.61) and rTNSS (7.96, 7.87). While the 24-hour iTNSS over the 4-week double-blind period was numerically improved with NASACORT AQ (-2.28) vs. placebo (-1.92), the difference was not statistically significant (difference from placebo -0.36; 95% CI [-0.77, 0.06]; p value = 0.095). For the 24-hour rTNSS over the 4 week double-blind treatment period, NASACORT A Q 110 mcg once daily provided statistically significantly greater improvement from baseline (-2.31) versus placebo (-1.87) (difference from placebo - 0.44; 95% CI [-0.84, -0.04]; p value = 0.033).

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

NASACORT AQ Nasal Spray, 55 mcg per spray, is supplied in a white high-density polyethylene container with a metered-dose pump unit, white nasal adapter, and patient instructions (NDC 0075-1506-16).

The contents of one 16.5 gram bottle provide 120 actuations. After 120 actuations, the amount of triamcinolone acetonide delivered per actuation may not be consistent and the unit should be discarded. Each actuation delivers 55 mcg triamcinolone acetonide from the nasal actuator after an initial priming of 5 sprays [see *Dosage and Administration Information* (2.3)].

In the Patient Package Information, patients are provided with a check-off form to track usage [see *Patient Counseling Information* (17)].

**Keep out of reach of children. Rx only**

## **16.2 Storage**

Store at Controlled Room Temperature, 20 to 25°C (68 to 77°F)

## **17. PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Patient Information and Instructions for Use).

### **17.1 Local Nasal Effects**

Patients should be informed that treatment with NASACORT AQ Nasal Spray may lead to adverse reactions, which include epistaxis and nasal ulceration. Candida infection may also occur with treatment with NASACORT AQ Nasal Spray. In addition, nasal corticosteroids are associated with nasal septal perforation and impaired wound healing. Patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use NASACORT AQ Nasal Spray until healing has occurred [*see Warnings and Precautions (5.1)*].

### **17.2 Cataracts and Glaucoma**

Patients should be informed that glaucoma and cataracts are associated with nasal and inhaled corticosteroid use. Patients should inform his/her health care provider if a change in vision is noted while using NASACORT AQ Nasal Spray [*see Warnings and Precautions (5.2)*].

### **17.3 Immunosuppression**

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections, or ocular herpes simplex [*see Warnings and Precautions (5.3)*].

### **17.4 Effect on Growth**

Parents should be advised that NASACORT AQ Nasal Spray may slow growth in children. A child taking NASACORT AQ Nasal Spray should have his/her growth checked regularly [*see Warnings and Precautions (5.5) and Pediatric Use (8.4)*].

### **17.5 Use Daily for Best Effect**

Patients should use NASACORT AQ Nasal Spray on a regular once-daily basis for optimal effect. It is also important to shake the bottle well before each use. Do not blow your nose for 15 minutes after using the spray. NASACORT AQ Nasal Spray, like other corticosteroids, does not have an immediate effect on rhinitis symptoms. Although improvement in some patient symptoms may be seen within the first day of treatment, maximum benefit may not be reached for up to one week. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

### **17.6 Keep Spray Out of Eyes**

Patients should be informed to avoid spraying NASACORT AQ Nasal Spray in their eyes.

**IMPORTANT:** Please read these instructions carefully before using your NASACORT® AQ Nasal Spray

**Patient Information**  
**Nasacort® AQ** (na' za-cort)  
(triamcinolone acetonide)  
**Nasal Spray**

**These instructions provide important information about Nasacort AQ. Ask your healthcare provider or pharmacist if you have any questions.**

**Important: For use as a nasal spray only.**

**What is Nasacort AQ?**

Nasacort® AQ Nasal Spray is a prescription medicine called a corticosteroid used to treat nasal symptoms of seasonal and year around allergies in adults and children 2 years of age and older. When Nasacort AQ is sprayed in your nose, this medicine helps to lessen the symptoms of sneezing, runny nose, nasal itching and stuffy nose.

Nasacort AQ is not for children under the age of 2 years.

**Who should use Nasacort AQ?**

**Do not use Nasacort AQ if you** have had a reaction to triamcinolone acetonide or to any of the other ingredients in Nasacort AQ. See the end of this leaflet for a complete list of ingredients in Nasacort AQ.

**What should I tell my healthcare provider before using Nasacort AQ?**

**Tell your healthcare provider if you are:**

- pregnant or planning to become pregnant
- breastfeeding
- exposed to chickenpox or measles
- feeling unwell or have any symptoms that you do not understand

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

**How do I use Nasacort AQ?**

- Use Nasacort AQ exactly as your healthcare provider tells you.
- You will get the best results if you use Nasacort AQ regularly and without missing a dose. Do not take extra doses.

- Nasacort AQ should be used as a nasal spray only. Do not spray it in your eyes or mouth.
- Your healthcare provider will tell you how and when to use Nasacort AQ. Do not use more Nasacort AQ or take it more often than your healthcare provider tells you.
- The prescription label will usually tell you how many sprays to take and how often. If it does not or if you are unsure, ask your healthcare provider or pharmacist.
  - **For people aged 12 years and older**, the usual dose is **2 sprays in each nostril, one time each day**.
  - **For children aged 6 to 12 years**, the usual dose is **1 spray in each nostril, one time each day**. Your healthcare provider may tell you to take 2 sprays in each nostril **one time each day**.
  - **For children aged 2 to 5 years**, the usual dose is **1 spray in each nostril, one time each day**.
  - **An adult should help a young child use this medicine.**

Do not stop taking Nasacort AQ without telling your healthcare provider. Before you throw away Nasacort AQ, talk to your healthcare provider to see if you need another prescription. If your healthcare provider tells you to continue using Nasacort AQ, throw away the empty or expired bottle and use a new bottle of Nasacort AQ.

- For detailed instructions, see the “Instructions for Use” at the end of this leaflet.
- Some symptoms may get better on the first day of treatment. It generally takes one week of use to feel the most benefit.
- Protect your eyes from the spray. If you get the spray in your eyes, rinse your eyes well with water.
- If your symptoms do not improve, or if they become worse, contact your healthcare provider.
- Tell your healthcare provider if you have irritation, burning or stinging inside your nose that does not go away when using Nasacort AQ.

### **What are the possible side effects of Nasacort AQ?**

Common side effects of Nasacort AQ include:

**Sore throat, headache, and nosebleeds.** If you have an increase in nosebleeds after using Nasacort AQ or the inside of your nose hurts, contact your healthcare provider.

### **What are the other risks of using Nasacort AQ?**

**Hole in the cartilage inside the nose (nasal septal perforation).** Tell your healthcare provider if you have a whistling sound from your nose when you breathe.

### **Fungal infection in your nose.**

**Slow wound healing.** You should not use Nasacort AQ until your nose has healed if you have a sore in your nose, if you have had surgery on your nose, or if your nose has been injured.

**Eye problems such as glaucoma and cataracts.** Tell your healthcare provider if you have a change in vision or have a history of increased intraocular pressure, glaucoma, or cataracts.

**Immune system problems that may increase your risk of infections.** You are more likely to get infections if you take medicines that weaken your body's ability to fight infections. Avoid contact with people who have contagious diseases such as chicken pox or measles while using Nasacort AQ. Symptoms of infection may include fever, pain, aches, chills, feeling tired, nausea and vomiting.

**Effect on how fast children grow.** Nasacort AQ may cause your child's growth to slow down. If your child is taking Nasacort AQ, your healthcare provider will need to regularly check the height of your child and adjust the dose as appropriate.

These are not all the possible side effects of Nasacort AQ. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

### **Instructions for Use**

Read these instructions carefully before using your Nasacort AQ.

#### **Before using the spray pump bottle:**

1. Pull the blue cover and remove the clip from the spray pump unit. See figure A.

If the top part of the spray pump comes off of the bottle when removing the cover, then re-insert the stem back into the pump.



**Figure A.**

2. Shake the spray pump bottle before each use.

### Priming the Spray Pump Bottle

3. Before using the spray pump bottle for the first time, it must be primed. To prime, put your thumb on the bottom of the bottle and your index and middle fingers on the “shoulders” of the bottle, and hold it upright. See figure B.



Figure B

4. Point the bottle away from your eyes. Push the bottle up with your thumb and against your two fingers **firmly** and **quickly** until a fine spray appears. Do this pumping action 5 times. Now your spray pump bottle is primed and ready for use.  
A fine mist can only be made by a rapid and firm pumping action.
5. Repeat priming the pump, if it has not been used for more than 2 weeks. To reprime, shake the spray pump bottle and pump it just one time. Now the spray pump bottle is reprimed.

### Using the spray:

6. Gently blow your nose to clear it, if needed. For small children, be sure to help them gently blow their nose, as much as possible.
7. Pull off the blue cover and clip as shown in figure C. Shake the spray pump well.



Figure C

8. Hold the spray pump firmly, with the index and middle finger on either side of the spray tip. Place your thumb on the bottom of the bottle. **Be careful** so that your fingers will not slip off the spray pump as you spray inside your nose. See figure D.





Figure D

9. Put the spray tip into one side of your nose. The tip should not reach far into the nose. Rest the side of your index finger against your upper lip. Tip your head back a little and aim the spray toward the back of your nose. See figure E.



Figure E

10. Press against the other side of your nose with your finger so the nostril is closed. Pump the spray bottle by pushing on the bottom of the bottle with your thumb **firmly** and **quickly** for the full dose of medicine. Sniff gently at the same time to help the medicine get to the back of your nose. See figure F. Repeat this step for the other side.



Figure F

11. Repeat steps 8, 9 and 10 if your healthcare provider tells you to use more than one spray in each nostril.
12. Do not blow your nose for 15 minutes after using the spray.
13. After use, wipe the nozzle on the spray bottle with a clean tissue, and replace the blue cover.
14. Keep the cover and the clip on the spray pump bottle when not in use.

### **Cleaning the spray pump bottle:**

**15.** To clean the spray pump bottle, remove the blue cover and the spray nozzle only. Soak the cover and spray nozzle in warm water for a few minutes, and then rinse under cold water. See figure G.



**Figure G**

**16.** Shake or tap off the excess water and allow to air dry. Once the cap and spray nozzle are dry, put the nozzle back onto the bottle, and prime the bottle as necessary until a fine mist is made. Use the spray as directed by your healthcare provider.

### **If the spray bottle does not work:**

The hole in the tip of the nozzle may be blocked. Never try to unblock the spray hole or enlarge it with a pin or other sharp object. This will make the spray mechanism not work correctly. Changing the size of the opening can change the amount of medicine you or your child will receive. This could cause an overdose of the medicine. To clean nasal spray pump bottle, refer to Step 15.

### **Important information**

Repriming the spray pump is only necessary when it has not been used for more than 2 weeks. To reprime, shake the bottle and only pump the spray bottle one time. Do not reprime if you use the spray more often than every two weeks.

Each Nasacort AQ bottle contains 120 doses of medicine plus a little extra for priming the pump. A check-off chart is included with your Nasacort AQ to help you keep track of the number of sprays. This will help make sure that you receive 120 sprays of Nasacort AQ.

- Keep this chart near your Nasacort AQ.
- Check off one circle each time you use this bottle of Nasacort AQ.
- When you reach 120 sprays, throw the bottle away.
- If you use more than 120 sprays, you will not get the right amount of medicine.

### Nasacort® AQ 120 Spray Check-Off

1	2	3	4	5	6	7	8
9	10	11	12	13	14	15	16
17	18	19	20	21	22	23	24
25	26	27	28	29	30	31	32
33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48
49	50	51	52	53	54	55	56
57	58	59	60	61	62	63	64
65	66	67	68	69	70	71	72
73	74	75	76	77	78	79	80
81	82	83	84	85	86	87	88
89	90	91	92	93	94	95	96
97	98	99	100	101	102	103	104
105	106	107	108	109	110	111	112
113	114	115	116	117	118	119	120

### How should I store Nasacort AQ?

- Store Nasacort AQ between 68° to 77°F (20° to 25° C).
- After using 120 sprays, throw the medicine away, as directed by your healthcare provider, even if the bottle is not empty. You may not get enough medicine if you use the bottle after 120 sprays.

### Keep Nasacort and all medicines out of the reach of children. General information about the safe and effective use of Nasacort AQ.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information. Do not use Nasacort AQ for a condition for which it was not prescribed. Do not give Nasacort AQ to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about Nasacort AQ. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Nasacort AQ that is written for health professionals.

For more information call 1-800-633-1610.

### What are the ingredients in Nasacort AQ?

Active ingredient: triamcinolone acetoneide

Inactive ingredients: Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, dextrose, benzalkonium chloride, and edetate disodium are contained in this aqueous medium; hydrochloric acid or sodium hydroxide may be added to adjust the pH to a target of 5.0 within a range of 4.5 and 6.0.

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