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*APPLICATION NUMBER:*  
**20-120**

**PHARMACOLOGY REVIEW**

Division of Pulmonary and Allergy Drug Products

DEC 13 1999

Review of Pharmacology/Toxicology Data

Submission: Revised labeling

Reviewer : VEWhitehurst

Review Date Completion : November 29, 1999

Information to be Conveyed to the Sponsor: Yes- revised labeling

HFD: HFD 570

NDA: NDA 20-120

Sponsor: Muro Pharmaceuticals, Inc

Drug: Tri-Nasal Spray (triamcinolone acetonide nasal solution)

Category: Steroid

Indication: Treatment of seasonal and perennial allergic rhinitis symptoms.

Route of Administration: Intranasal

Dose: Maximum daily dose is 400 µg or 8 µg/kg for a 50 kg person.

**Introduction and History:**

Revised labeling for Tri-Nasal Spray (triamcinolone acetonide).

**Labeling:**

The labeling for Tri-Nasal Spray should be revised as follows:

**Carcinogenesis, Mutagenesis and Impairment of Fertility:**

In two-year ~~triamcinolone acetonide~~ triamcinolone acetonide did not increase the incidence of tumors at oral doses up to 1 and 3 mcg/kg, respectively (less than the maximum recommended daily intranasal dose on a mcg/m<sup>2</sup> basis).

The genotoxic potential of triamcinolone acetonide has not been studied.

Triamcinolone acetonide did not impair fertility in rats given oral doses up to 15 mcg/kg (less than the maximum recommended daily intranasal dose on a mcg/m<sup>2</sup> basis). However, triamcinolone acetonide caused increased fetal resorptions and stillbirths and decreased pup weight and survival at 5 mcg/kg (less than the maximum recommended daily intranasal dose on a mcg/m<sup>2</sup> basis). These effects were not produced at 1 mcg/kg (less than the maximum recommended daily intranasal dose on a mcg/m<sup>2</sup> basis).

**Pregnancy: Pregnancy Category C:**

First paragraph:

Triamcinolone acetonide induced cleft palate, internal hydrocephaly and skeletal defects in fetuses of rats and rabbits treated throughout organogenesis with daily inhalation doses of 20 mcg/kg (less than the maximum recommended daily intranasal dose on a mcg/m<sup>2</sup> basis).

Triamcinolone acetonide induced cranial malformations in fetuses of Rhesus monkeys treated throughout organogenesis with daily intramuscular doses of 500 mcg/kg and greater (approximately 20 times the maximum recommended daily intranasal dose on a mcg/m<sup>2</sup> basis). The 500 mg/kg dose was the lowest dose used in this study.

**Overdosage Section:**

Add as last sentence:

The intranasal median lethal dose has not been determined in animals.

**Comments:**

The names of the animal species should be included in the labeling, i.e., Sprague-Dawley rats, New Zealand White rabbits, etc.

**Recommendations:**

Please send labeling revisions to the sponsor.

Virgil Whitehurst  
Pharmacologist

12-13-99

CC: Div File  
HFD-570/RHuff  
HFD-570/VWhitehurst  
HFD-570/SBarnes

/S/ 12-13-99

DEC 15 1999

Division of Pulmonary and Allergy Drug Products

Review of Pharmacology/Toxicology Data

Chemistry Consult: Chemistry consult dated December 13, 1999

Reviewer: VEWhitehurst

Review Date Completion: December 14, 1999

Information to be Conveyed to the Sponsor: No

HFD: HFD 570

NDA: NDA 20-120

Sponsor: Muro Pharmaceuticals, Inc

Drug: Tri-Nasal Spray (triamcinolone acetonide nasal solution)

Category: Steroid

Indication: Treatment of seasonal and perennial rhinitis.

Route of Administration: Intranasal

Dose: Maximum daily dose is 400 µg or 8 µg/kg for a 50 kg person.

**Introduction and History:**

This review is to respond to a chemistry consult (attached) requested by Dr. Chong-Ho Kim, review chemist in HFD 570, to evaluate the responses of the sponsor to the recommendations in the pharmacologist's review stamp dated November 12, 1999.

1. Based on the revised specification, the daily \_\_\_\_\_ exposure in Tri-Nasal is approximately \_\_\_\_\_  $\mu\text{g}/\text{day}$ . The improved specification is acceptable and ensures an acceptable level of risk (i.e., less than  $10^{-5}$  risk of carcinogenicity; an exposure of \_\_\_\_\_  $\mu\text{g}/\text{day}$  is associated with a  $10^{-5}$  risk).

2. The sponsor's ongoing endeavor to improve the detection limit for \_\_\_\_\_ and \_\_\_\_\_ is acceptable. We acknowledge that the \_\_\_\_\_ profile is likely reflected in the profile for \_\_\_\_\_ so it is unlikely that the actual levels of \_\_\_\_\_ and \_\_\_\_\_ pose a risk (i.e., \_\_\_\_\_ and \_\_\_\_\_ do not likely contribute notably more to the \_\_\_\_\_ from \_\_\_\_\_ than they do to the \_\_\_\_\_ associated with \_\_\_\_\_), given that the specification for total \_\_\_\_\_ is acceptable. It is merely a matter of improving the sensitivity of detection. Ideally, the limit of detection for \_\_\_\_\_ and \_\_\_\_\_ should ensure that exposures are \_\_\_\_\_  $\mu\text{g}/\text{day}$  and \_\_\_\_\_  $\mu\text{g}/\text{day}$ , respectively. However, if such limits of detection are not achievable, the current specifications can be accepted based on the acceptability of the specification for total \_\_\_\_\_

3. The commitment to conduct two in-vitro genotoxicity studies (one for mutagenicity and one for chromosomal aberrations) to support the request for a \_\_\_\_\_ specification for the impurity \_\_\_\_\_ is acceptable. (Note: These studies will be necessary to support any specification greater than \_\_\_\_\_) However, the results of these studies should be submitted to the FDA within six months of the application approval.

/S/  
Virgil Whitehurst  
Pharmacologist 12-15-99

CC :  
Division File  
HFD-570/RHuff /S/ JJ 12-15-99

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**APPEARS THIS WAY  
ON ORIGINAL**

Division of Pulmonary Drug Products

Review of Pharmacology and Toxicology Data

NDA : NDA 20-120 -Amendment dated 4-14-1997

Sponsor : Muro Pharmaceuticals, Inc  
890 East Street  
Tewksbury, MA 01876-1496

Drug : Tri- Nasal Nasal Spray (triamcinolone acetonide nasal solution)

Category : Steroid

Daily Dose : Maximum daily dose is 400  $\mu$ g or 8  $\mu$ g/kg for a 50 kg person.

Submission : Chemistry consult to evaluate in vivo biological test data for the plastic in the tri- nasal bottle and spray pump.

**Review of the Biological Reactivity Tests for Plastics in the tri-nasal bottle:**

- 1. USP Biological Reactivity Tests in Vivo for Plastics , Class V, Intracutaneous Test and Systemic Injection Test. ( Studies carried out by \_\_\_\_\_**

Study Number : 203010-03

GLP statement : satisfactory

Study Initiation : 10/24/96

Study completion : 2/20/97

**Methods :**

The tests were carried out using the tri-nasal bottle, 20 ml amber PET, Muro control number 07595. The test material was subdivided into pieces suitable for extraction and extracted at 50 ° C for 72 hours with :

1. 20 ml, sodium chloride injection solution
2. 20 ml, sesame oil
3. 20 ml, 1/20 solution of alcohol in sodium chloride injection
4. 20 ml, polyethylene glycol 400 (PEG).

Appropriate blanks (extraction solution only) were prepared in the same manner.

**Intracutaneous Injection Test :**

Two rabbits (New Zealand male and female) were injected intracutaneously (0.2 ml) at 5 sites on one side with the sample extract and on the other side with the appropriate blank. The injection sites were examined for 72 hours for gross evidence of tissue reaction.

**Results :**

All rabbits were normal. None of the injection sites showed any gross tissues reactions due to extracts.

**Systemic Injection Tests :**

5 males, Swiss Webster mice per group were injected with extracts or the appropriate blanks and observed for 72 hours after injections. Sodium chloride and the alcohol solution were injected via the tail vein (50 ml/kg) while the sesame oil and the PEG were administered ip.

**Results :**

All mice were normal. None of the mice died or appeared to be ill due to injections.

**2.USP Biological Reactivity Tests in Vivo for Plastics , Class V,  
Intracutaneous Test and Systemic Injection Test. ( studies carried  
out by \_\_\_\_\_**

Study Number : x5k195G and x5k196G

GLP statement : satisfactory

Study Initiation : 11/29/95

Study completion : 12/19/95

**Methods :**

The tests was carried out using the tri-nasal pump, \_\_\_\_\_ The test material was subdivided into 150 pieces suitable for extraction and extracted at 50 ° C for 72 hours with ;

1. 20 ml, sodium chloride injection solution
2. 20 ml, sesame oil
3. 20 ml, 1/20 solution of alcohol in sodium chloride injection
4. 20 ml, polyethylene glycol 400 (PEG).

Appropriate blanks (extraction solution only) were prepared in the same manner.

**Intracutaneous Injection Test :**

Two rabbits ( New Zealand male and female) were injected intracutaneously (0.2 ml) at 5 sites on one side with the sample extract and on the other side with the appropriate blank. The injection sites were examined for 72 hours for gross evidence of tissue reaction.

**Results :**

All rabbits were normal. None of the injection sites showed any gross tissues reactions due to extracts.

**Systemic Injection Tests :**

5 males, Swiss Webster mice per group were injected with extracts or the appropriate blanks and observed for 72 hours after injections. Sodium chloride and the alcohol solution were injected via the tail vein (50 ml/kg) while the sesame oil and the PEG were administered ip.

**Results :**

All mice were normal. None of the mice died or appeared to be ill due to injections.

**3.USP Biological Reactivity Tests in Vivo for Plastics , Class V, Intracutaneous Test and Systemic Injection Test. (Studies carried out by \_\_\_\_\_)**

Study Number : x4L320 and x4L321

GLP statement : satisfactory

Study Initiation : 1/20/95

Study completion : 1/31/95

**Methods :**

The tests was carried out using clear plastic material, (lot # 3,4335,7). The test material was subdivided into 52 pieces suitable for extraction and extracted at 50 ° C for 72 hours with :

1. 20 ml, sodium chloride injection solution
2. 20 ml, sesame oil
3. 20 ml, 1/20 solution of alcohol in sodium chloride injection
4. 20 ml, polyethylene glycol 400 (PEG).

Appropriate blanks (extraction solution only) were prepared in the same manner.

**Intracutaneous Injection Test :**

Two rabbits (New Zealand male and female) were injected intracutaneously (0.2 ml) at 5 sites on one side with the sample extract and on the other side with the appropriate blank. The injection sites were examined for 72 hours for gross evidence of tissue reaction.

**Results :**

All rabbits were normal. None of the injection sites showed any gross tissues reactions due to extracts.

**Systemic Injection Tests :**

5 females, Swiss Webster mice per group were injected with extracts or the appropriate blanks and observed for 72 hours after injections. Sodium chloride and the alcohol solution were injected via the tail vein (50 ml/kg) while the sesame oil and the PEG were administered ip.

**Results:**

All mice were normal. None of the mice died or appeared to be ill due to injections.

**4.USP Biological Reactivity Tests in Vivo for Plastics , Class V, Intracutaneous Test and Systemic Injection Test. (Studies carried out by \_\_\_\_\_)**

Study Number : X5k193G and x 5k194G

GLP statement : satisfactory

Study Initiation : 11/29/95

Study completion : 12/19/95

Methods :

The tests was carried out using plaatic materials, lot # 2008600000. The pieces were extracted at 50 ° C for 72 hours with ;

1. 20 ml, sodium chloride injection solution
2. 20 ml, sesame oil
3. 20 ml, 1/20 solution of alcohol in sodium chloride injection
4. 20 ml, polyethylene glycol 400 (PEG).

Appropriate blanks (extraction solution only) were prepared in the same manner.

#### **Intracutaneous Injection Test :**

Two rabbits (New Zealand male ) were injected intracutaneously (0.2 ml) at 5 sites on one side with the sample extracts and on the other side with the appropriate blanks. The injection sites were were examined for 72 hours for gross evidence of tissue reaction.

#### **Results :**

All rabbits were normal. None of the injection sites showed any gross tissues reactions due to extracts.

#### **Systemic Injection Tests :**

5 males, Swiss Webster mice per group were injected with extracts or the appropriate blanks and observed for 72 hours after injections. Sodium chloride and the alcohol solution were injected via the tail vein (50 ml/kg) while the sesame oil and the PEG were administered ip.

#### **Results :**

All mice were normal. None of the mice died or appeared to be ill due to injections.

**5.USP Biological Reactivity Tests in Vivo for Plastics , Class V, Intracutaneous Test and Systemic Injection Test. (Studies carried out by \_\_\_\_\_)**

Study Number : x4L318 and x4L316

GLP statement : satisfactory

Study Initiation : 1/20/95

Study completion : 1/31/95

**Methods :**

The tests was carried out using clear plastic, lot # 3,4313,2. The pieces were extracted at 50 ° C for 72 hours with :

1. 20 ml, sodium chloride injection solution
2. 20 ml, sesame oil
3. 20 ml, 1/20 solution of alcohol in sodium chloride injection
4. 20 ml, polyethylene glycol 400 (PEG).

Appropriate blanks (extraction solution only) were prepared in the same manner.

**Intracutaneous Injection Test :**

Two rabbits (New Zealand male ) were injected intracutaneously (0.2 ml) at 5 sites on one side with the sample extract and on the other side with the appropriate blank. The injection sites were examined for 72 hours for gross evidence of tissue reaction.

**Results :**

All rabbits were normal. None of the injection sites showed any gross tissues reactions due to extracts.

**Systemic Injection Tests :**

5 males, Swiss Webster mice per group were injected with extracts or the appropriate blanks and observed for 72 hours after injections. Sodium chloride and the alcohol solution were injected via the tail vein (50 ml/kg) while the sesame oil and the PEG were administered ip.

**Results :**

All mice were normal. None of the mice died or appeared to be ill due to injections.

**Evaluation :**

USP biological reactivity tests were carried out using clear plastic materials, the PET amber nasal bottle, the nasal pump heads and the plastic cylinders. The plastic materials were subdivided into small pieces and extracted with sodium chloride, alcohol solution, sesame oil and PEG 400 for 72 hours at 50 ° C. The extracted solutions was injected into rabbits intracutaneously and into mice intraperitoneously and intravenously. There were no gross tissue reactions, deaths or morbidities due to the injection of the plastic materials.

**Conclusion :**

Plastic materials used in the bottle and the cylinder head are reasonably safe.

**/S/**

Virgil Whitehurst  
Pharmacologist

9-8-97

CC : Original NDA  
HFD -570/Divfile  
HFD-570/VEW  
HFD-570/LNG  
HFD-570/HSheevers  
HFD-570/Sbarnes  
HFD-570/Medofficer

**/S/**

9/8/97

N:/NDA/20-120/pharm/04-14-97.rev

**APPEARS THIS WAY  
ON ORIGINAL**

NOV 1 1999

Barnes

Division of Pulmonary and Allergy Drug Products

Review of Pharmacology/Toxicology Data

Chemistry Consult : Chemistry consult dated September 27, 1999

Reviewer : VEWhitehurst

Review Date Completion : October 20, 1999

Information to be Conveyed to the Sponsor: No

HFD: HFD 570

NDA: NDA 20-120

Sponsor: Muro Pharmaceuticals, Inc

Drug: Tri-Nasal Spray (triamcinolone acetonide nasal solution)

Category: Steroid

Indication: Treatment of seasonal and perennial rhinitis.

Route of Administration: Intranasal

Dose: Maximum daily dose is 400 µg or 8 µg/kg for a 50 kg person.

**Introduction and History:**

This review is to respond to a chemistry consult (attached) requested by Dr. Chong-Ho Kim, review chemist in HFD 570, to evaluate the safety of            pump and            extractables.

Extractions were performed using water, alcohol and hexane. The alcohol extraction was used to determine the daily exposures to the extractables because polyethylene and propylene glycols are present in the drug formulation.

Dr. Kim also asked for an evaluation of the safety of the proposed specification of \_\_\_\_\_ an impurity, and of the \_\_\_\_\_ concentration of \_\_\_\_\_ used as \_\_\_\_\_

**Extractables from the \_\_\_\_\_**

The µg/day exposures tabulated below are twice those presented in the sponsor's submission. The sponsor's calculations were based on the typical triamcinolone acetonide dose of 200 µg (2 sprays per nostril); however, the maximum dose is 400 µg (4 sprays per nostril).

**Pump Components:**

Extractable	µg/day*	µg/kg	ng/kg**

\*Based on the maximum daily dose of 400 µg.

\*\*Calculated by dividing the µg/day by 50 kg and converted to nanograms (multiplied by 1000).

**Comments:**

The daily exposure to \_\_\_\_\_ is acceptable because the exposure is \_\_\_\_\_ ng/kg and \_\_\_\_\_ contains no structural alerts for either irritancy or genotoxicity/carcinogenicity. The rationale for the \_\_\_\_\_ ng/kg

limit is provided in the attached "Proposed Approach for Qualifying Extractables/Leachables from MDIs."

The daily exposure to \_\_\_\_\_ exceeds \_\_\_\_\_ ng/kg, necessitating qualification. Although there are no acute toxicity data, the sponsor cites a 10 day rat teratology study in which the oral NOAEL was 150 mg/kg/day (study submitted by \_\_\_\_\_ to EPA, \_\_\_\_\_). Although the study duration does not adequately cover chronic clinical use and examined parameters did not likely include clinical pathology or histopathology, the NOAEL dose was so much greater than the \_\_\_\_\_ ng/kg/day clinical exposure that it seems reasonable to assume that systemic toxicity is likely to be minimal. Furthermore, any pulmonary irritation is likely to be limited because the particle size for a nasal spray is generally greater than \_\_\_\_\_ microns, reducing the potential for the drug solution to reach respiratory tissues (see reference to conversation with Dr. Badrul Chowdhury later in this review).

The daily exposure to \_\_\_\_\_ exceeds \_\_\_\_\_ ng/kg, necessitating qualification. Furthermore, \_\_\_\_\_ is structurally similar to \_\_\_\_\_ which is known to be an irritant. \_\_\_\_\_ is, however, approved as an excipient in inhalation drugs at daily exposures up to \_\_\_\_\_ ng/kg (NDA 20-503). Based on the structural similarity of \_\_\_\_\_, it may be reasonable to assume they have similar systemic toxicity profiles. Thus, exposures of up to \_\_\_\_\_ ng/kg/day would be acceptable. The projected exposure for \_\_\_\_\_ exceeds \_\_\_\_\_ ng/kg/day (\_\_\_\_\_ ng/kg/day), but may be acceptable based on two factors. First, \_\_\_\_\_ is an endogenous substance in body fluids. Second, the particle size of the nasal spray is generally greater than \_\_\_\_\_ microns, which reduces the likelihood of lung deposition and subsequent systemic absorption. The latter argument may also diminish concern about potential pulmonary irritancy (see reference to conversation with Dr. Badrul Chowdhury later in this review). If the potential irritancy of \_\_\_\_\_ remains a clinical concern, the relative topical irritancy of \_\_\_\_\_ and \_\_\_\_\_ could be compared and results extrapolated for respiratory irritancy.



\*Based on the maximum daily dose of 400  $\mu\text{g}$ .

\*\*Calculated by dividing the  $\mu\text{g}/\text{day}$  by 50 kg and converted to nanograms (multiplied by 1000).

**Comments:**

The projected daily exposure to total \_\_\_\_\_ is unacceptable. Based on \_\_\_\_\_ inhalation risk factor of  $2.5\text{E}-4$  per  $\text{ng}/\text{kg}/\text{day}$  of \_\_\_\_\_, the \_\_\_\_\_  $\text{ng}/\text{kg}/\text{day}$  exposure is associated with a risk of  $1.5\text{E}-5$ , whereas a maximum risk of  $1.0\text{E}-5$  (1 in 100,000 risk of cancer based on lifetime exposure) is deemed acceptable. In order to lower the risk factor to  $10^{-5}$ , the maximum acceptable daily exposure would have to be \_\_\_\_\_  $\text{ng}/\text{kg}/\text{day}$  or \_\_\_\_\_  $\mu\text{g}/\text{day}$  (NDA 20-236). The sponsor should improve the level of detection accordingly.

The \_\_\_\_\_  $\text{ng}/\text{kg}/\text{day}$  exposure to total \_\_\_\_\_ is acceptable, based on the risk factor derived for \_\_\_\_\_. Using a risk factor of  $2.2\text{E}-6$  per  $\text{ng}/\text{kg}/\text{day}$ , \_\_\_\_\_  $\text{ng}/\text{kg}/\text{day} \times 2.2\text{E}-6$  per  $\text{ng}/\text{kg}/\text{day} = \text{---} \text{E}-6$ , which is less than  $10^{-5}$  (a 1 in 100,000 risk of cancer based on lifetime exposure), which the Division has deemed an acceptable risk. Based on individual risk factors for \_\_\_\_\_,  $1.3\text{E}-4$ ,  $4.0\text{E}-6$  and  $1.0\text{E}-6$  per  $\text{ng}/\text{kg}/\text{day}$ , respectively, the exposure to \_\_\_\_\_ is acceptable, but the exposures to \_\_\_\_\_ result in a greater than  $10^{-5}$  risk (a  $10^{-5}$  risk would require exposure to be limited to \_\_\_\_\_  $\mu\text{g}/\text{day}$  for \_\_\_\_\_ and \_\_\_\_\_  $\mu\text{g}/\text{day}$  for \_\_\_\_\_).

Therefore, the limit of detection for \_\_\_\_\_ and \_\_\_\_\_ should be improved, if feasible. However, it is acknowledged that the \_\_\_\_\_ extraction profile is likely reflected in the profile for \_\_\_\_\_ so it is unlikely that the actual levels of \_\_\_\_\_ and \_\_\_\_\_ pose a risk (i.e., \_\_\_\_\_ and \_\_\_\_\_ do not likely contribute notably more to the \_\_\_\_\_ load extracted from the \_\_\_\_\_ than they do to the \_\_\_\_\_ load associated with \_\_\_\_\_).

**APPEARS THIS WAY  
ON ORIGINAL**

The sponsor has requested a specification of \_\_\_\_\_ for \_\_\_\_\_  
 \_\_\_\_\_ The qualification threshold for impurities in drug products with a daily dose of less than 10 mg is 1.0% (ICH Q3B guideline); therefore, there is no need to qualify this impurity for systemic toxicity. However, the \_\_\_\_\_ is a structural alert for genotoxicity. As such, the isolated impurity should be tested in in vitro genotoxicity assays, one for mutagenicity and one for chromosomal aberrations. If the NDA application is to be approved in this cycle, these tests may be completed as a Phase 4 commitment. A Phase 4 commitment is acceptable because in a "worst case" scenario in which the \_\_\_\_\_ poses a carcinogenicity risk similar to that for \_\_\_\_\_, the risk associated with the exposure to the \_\_\_\_\_ will still be less than  $10^{-5}$  (1% of the 400 ug/day maximum clinical dose = 4 ug/day of \_\_\_\_\_ = 4000 ng/day = 80 ng/kg/day, and the exposure to \_\_\_\_\_ associated with a  $10^{-5}$  risk is 310 ng/kg/day).

#### \_\_\_\_\_ Concentrations:

As part of the reformulation of the drug, the concentration of \_\_\_\_\_ was \_\_\_\_\_ from approximately \_\_\_\_\_. The chemistry consult requested information concerning the safety of \_\_\_\_\_. The major safety concerns are airway irritation and the potential to induce bronchospasms in the respiratory tissues. A review of NDAs with \_\_\_\_\_ reveals the following concentrations, all of which are less than the proposed \_\_\_\_\_

NDA	Drug Name	_____ Concentration
20-114	Astelin Nasal Spray	_____
20-762	Nasonex Nasal Spray	_____
20-409	Nasarel Nasal Spray	_____

I discussed the safety of \_\_\_\_\_ with Dr. Badrul Chowdhury, clinical team leader. Dr. Chowdhury believes that this concentration of \_\_\_\_\_ is reasonably safe. This conclusion is based on the fact that the drug

product is a solution and the major of the particles are greater than  $\sim$  microns, significantly reducing the potential for the solution to reach the respiratory tissues.

### Recommendations:

Bolded sections should be conveyed to the sponsor. For recommendation no. 2, depending on the clinical decision a comment may need to be sent to the sponsor.

1. The extractable specifications are acceptable for \_\_\_\_\_  
\_\_\_\_\_ It should be noted that the specific issue of nasal irritancy could not be addressed for some of the extractables, but nasal irritancy is considered to have less critical consequences than pulmonary irritancy, which was considered.
2. The extractable specification for \_\_\_\_\_ may be acceptable. \_\_\_\_\_ is structurally similar to \_\_\_\_\_ a know irritant. \_\_\_\_\_ is, however, approved as an excipient in inhalation drugs at daily exposures up to  $\sim$  ng/kg. Based on the structural similarity of \_\_\_\_\_ it may be reasonable to assume they have similar systemic toxicity profiles. Thus exposures of up to  $\sim$  ng/kg/day would be acceptable. The projected exposure for \_\_\_\_\_ exceeds  $\sim$  ng/kg/day ( $\sim$  ng/kg/day), but may be acceptable based on two factors. First, \_\_\_\_\_ is an endogenous substance in body fluids. Second, the particle size of the nasal spray is generally greater than  $\sim$  microns, which reduces the likelihood of lung deposition and subsequent systemic absorption. The latter argument may also diminish concern about potential pulmonary irritancy. If the potential irritancy of \_\_\_\_\_ remains a clinical concern, the relative topical irritancy of \_\_\_\_\_ and \_\_\_\_\_ could be compared and results extrapolated for respiratory irritancy.
3. The limit of detection for \_\_\_\_\_ is insufficient to ensure an acceptable level of risk (i.e.,  $10^{-5}$  risk of carcinogenicity). The level

of detection needs to be improved by one-third so as to limit daily exposures to — ng/kg/day or — µg/day.

4. The specification for total — is acceptable, based on risk calculations for —. However, the limit of detection for the individual — is not sufficient to ensure a risk of  $10^{-5}$  (a  $10^{-5}$  risk would require exposure to be limited to — µg/day for — and — µg/day for —). Therefore, the limit of detection for — should be improved, if feasible, so as to ensure that exposures are less than — µg/day for — and — µg/day for —. It is acknowledged that the — extraction profile is likely reflected in the profile for — so it is unlikely that the actual levels of — pose a risk (i.e., — do not likely contribute notably more to the — load extracted from the — than they do to the — load associated with —). It is merely a matter of the sensitivity of detection.
5. In order to support the requested — specification for the impurity — which contains a structural alert for mutagenicity, the sponsor should conduct two in vitro genotoxicity assays using the isolated impurity. One test should be for mutagenicity and the other for chromosomal aberrations. If the NDA application is to be approved in this cycle, these tests may be completed as a Phase 4 commitment. A Phase 4 commitment is acceptable because in a "worst case" scenario in which the — poses a carcinogenicity risk similar to that for —, the risk associated with the exposure to the — will still be less than  $10^{-5}$  (1% of the 400 ug/day maximum clinical dose = 4 ug/day of — = 4000 ng/day = 80 ng/kg/day, and the exposure to — associated with a  $10^{-5}$  risk is 310 ng/kg/day).

6. The \_\_\_\_\_ concentration of \_\_\_\_\_ in the new formulation is reasonably safe. This conclusion is based on the fact that the drug product is a solution, such that the majority of particles are greater than \_\_\_\_\_ microns in size, significantly reducing the potential for the solution to reach the respiratory tissues.

✓  
/S/ 6-4-99  
Virgil Whitehurst  
Pharmacologist

CC :  
Division File  
HFD-570/RHuff /S/ 11-1-99  
HFD-570/CKim ))  
HFD-570/VWhiteurst  
HFD-570/Sbarnes

**APPEARS THIS WAY  
ON ORIGINAL**

## Proposed Approach for Qualifying Extractables/Leachables from MDIs

The following recommendations are based on analysis of toxicity data in the EPA data bases (HEAST and IRIS).

1. All extractables/leachables should be assessed for mutagenic or carcinogenic potential. For known carcinogens inhalation carcinogenicity risk based on EPA slope factors, unit risk or similar calculations should be less than  $10^{-6}$ . Chemicals with negative mutagenic or carcinogenic test results are considered qualified. Chemicals that have not been tested for mutagenic or carcinogenic potential are qualified if they lack structural alerts for carcinogenicity or mutagenicity. Identification of structural alerts can be based on commercial software programs (e.g. DEREK, Case/Multicase, TOPKAT), or on published lists of structural alerts (e.g. Mutation Res., 223:73, 1989, or FDA/CVM *Guideline 3*, July 1994).

**Rationale:** The median virtually safe dose ( $10^{-6}$  risk) for — inhalation carcinogens was — ng/kg/day, 10-fold lower than the median daily exposure of — ng/kg/day for — leachables measured in 3 NDAs. Carcinogenicity data will not be available for most leachables. In the absence of carcinogenicity data, structural alerts can serve as a reasonable surrogate. Non-genotoxic carcinogens are less likely to be identified through this approach but those type of carcinogens often have higher thresholds for carcinogenic activity than genotoxic carcinogens.

2. For chemicals present at daily inhalation exposures less than 100 ng/kg there is no significant concern for systemic toxicity. Chemicals present at exposures greater than 100 ng/kg need to be qualified by data from preclinical studies with the MDI formulation, published toxicity data, or structural similarity to chemicals with known toxicity profile.

**Rationale:** Recommendation 1 is based on — chemicals with inhalation data (i.e. not extrapolated from oral data) and systemic target toxicity. The presumed safe dose based on the EPA reference concentration (RfC) was less than 100 ng/kg/day for only — chemicals — , all of which had a "safe" dose of — ng/kg/day. The safety factors built into these EPA estimates is large 1,000-fold or 10,000-fold below the NOAEL or LOAEL for these — chemicals.

3. For chemicals present at daily inhalation exposures less than 100 ng/kg there is no concern for respiratory tract toxicity unless there is a structural alert for a highly reactive irritant structure. Structural alerts would include isocyanates, aldehydes, organic acids, strained heterocyclic rings, and halogenated aromatic rings.

Chemicals with exposure greater than 100 ng/kg/day need to be qualified for respiratory tract toxicity as in recommendation #2.

**Rationale:** Recommendation 2 is based on — chemicals with inhalation data and respiratory tract target toxicity. Based on the RfC, the safe daily inhalation exposure was less than 100 ng/kg for — chemicals — This is again based on a relatively large safety factor (300-1000) and all of the chemicals whose safe exposure was less than 100 ng/kg/day had one of the obvious structural alerts described above.

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ON ORIGINAL**

AUG 20 1997

Division of Pulmonary Drug Products

Review and Evaluation of Pharmacology and Toxicology Data

NDA : 20,120

Submission : Supplement dated April 14, 1997

Date of the Review : August 14, 1997

Revised Review of Labeling : August 17, 1997

Sponsor : Muro Pharmaceuticals, Inc  
890 East Street, Tewksbury, MA 01876-1496

Drug : Tri-Nasal Spray (triamcinolone acetonide nasal solution)

Category : Steroid

Daily Dose : Maximum daily dose is 400 µg or 8 µg/kg for a 50 kg adult

Submission Content : Labeling changes as proposed by the sponsor.

**Review and Evaluation :**

The labeling for Tri-Nasal Spray should be revised as follows :

**Carcinogenesis, Mutagenesis and Impairment of Fertility:**

In a two year \_\_\_\_\_ triamcinolone acetate \_\_\_\_\_

There are no adequate and well-controlled studies in pregnant women. \_\_\_\_\_, triamcinolone acetonide should be used in pregnancy only if the potential benefit justifies the potential risk. 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 \_\_\_\_\_ production during pregnancy, most women will require a lower exogenous \_\_\_\_\_ dose and many will not need \_\_\_\_\_ treatment during pregnancy.

**Recommendation :**

We have reviewed the proposed changes in the carcinogenesis, impairment of

fertility and pregnancy sections and it is our conclusion that the labeling should be corresponded to the sponsor as proposed in this pharmacology review.

Calculations for the comparisons of the carcinogenesis, mutagenicity and impairment of fertility and pregnancy sections are as follows:

Dose times animal "k" factor divided by maximum recommended human dose times "k" factor

Carcinogenicity Studies :

Rat :

$$\frac{1.0 \times 6 = 6.0}{8 \times 37 = 296} = .02 \text{ or } 2/100 \text{ or } 1/50$$

Mouse :

$$\frac{3.0 \times 3.0 = 9}{8 \times 37 = 296} = .03 \text{ or } 3/100 \text{ or } 1/30$$

Impaired Fertility :

Rat :

$$\frac{15 \times 6 = 90}{8 \times 37 = 296} = .3 \text{ or } 3/10 \text{ or } 1/3$$

$$\frac{5.0 \times 6 = 30}{8 \times 37 = 296} = .1 \text{ or } 1/10$$

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ON ORIGINAL**

$$\frac{1.0 \times 6 = 6}{8 \times 37 = 296} = .02 \text{ or } 2/100 \text{ or } 1/50$$

Pregnancy Section :

Rat :

$$\frac{20 \times 6 = 120}{8 \times 37 = 296} = .4 \text{ or } 2/5$$

4

Rabbit :

$$\underline{20 \times 12 = 240 = .8 \text{ or } 4/5}$$

$$8 \times 37 = 296$$

Monkey :

$$\underline{500 \times 12 = 6000 = 20.2}$$

$$8 \times 37 = 296$$

/S/

Virgil Whitehurst  
Pharmacologist  
CC : Orig NDA  
HFD-570/Divfile  
HFD-570/VEW  
HFD-570/Kwong  
HFD-570/Sheevers  
HFD-571/Barnes

8/20/97

/S/  
8/20/97

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JUL 16 1996

Division of Pulmonary Drug Products

Review of Pharmacology and Toxicology Data

NDA 20-120

Review : Original Review

Information to be Conveyed to the Sponsor : Yes

Reviewer : VEWhitehurst

Date Submitted : April 1, 1996

Date Review Completion : July 8, 1996

Date Revised : July 13, 1996

Sponsor : Muro Pharmaceutical Inc  
890 East Street  
Tewksbury, MA 01876

Drug : Tri-nasal Spray (triamcinolone acetonide nasal solution 0.05%)

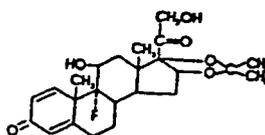
Category : Steroid

Chemical Name : 9-Fluoro-11 $\beta$ , 16 $\alpha$ , 17,21-tetrahydroxy pregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with acetone

Molecular Formula : C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>

Molecular Weight : 434.51

Chemical Structure :



Components of Tri-nasal Spray

<u>Components</u>	<u>Composition</u>		<u>batch</u>
	<u>g/100 ml</u> <u>(%)</u>	<u>per spray</u>	
Triamcinolone acetonide	0.05	50 µg	
Propylene glycol			
Polyethylene glycol			
Edetate disodium			
Citric acid			
Sodium citrate			
<hr/>			
<hr/>			
— Benzalkonium chloride			
Purified water			
Totals			

\_\_\_\_\_ may be used to adjust the pH. \*\* Totals for composition, g/100 ml, per spray, and \_\_\_\_\_ batch exceeds 100%. I notified the reviewing chemist, Dr Linda Ng of our concerns.

Indication : The treatment of seasonal and perennial rhinitis symptoms

Route of Administration : Intranasal

Daily Dosage : — - 400 µg once daily or - - 8 µg/kg for a 50 kg person

**Preclinical Data :**

There were no preclinical data submitted in this NDA. However, FDA has concluded that this NDA may be considered a 505 (b) (2) submission. As a 505 (b) (2) NDA, the sponsor can reference the safety and efficacy of an approved NDA, NDA 20-468, Nasacort AQ (pharmacology review attached) and/or NDA 19798, Nasacort-pediatric solution.

Conclusion : The NDA is approvable from the standpoint of pharmacology pending revised labeling and environmental assessment.

The following labeling revisions are recommended for Tri-Nasal Spray :

**Clinical Pharmacology section : (5 th paragraph)**

In animals studies using rats and dogs, three metabolites of triamcinolone acetonide have been identified. They are 6 $\beta$ -hydrotriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6 $\beta$ -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.

**Carcinogenesis, Mutagenesis and Impairment of Fertility section :**

Carcinogenesis, Mutagenesis :

┌

Impairment of Fertility :

┌

└

└

\_\_\_\_\_ increases in fetal resorptions and stillbirths and decreases in pup body weight and survival at \_\_\_\_\_ of 5.0 mcg/kg \_\_\_\_\_

**Pregnancy : Pregnancy Category C :**

\_\_\_\_\_ There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetate should be used in pregnancy only if the potential benefits justifies the potential risk to the fetus. Since their introduction, experience with oral corticosteroids in pharmacologic as opposed to physiologic doses suggests that some rodents, \_\_\_\_\_ are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in \_\_\_\_\_ production during pregnancy, most women will require a lower exogenous \_\_\_\_\_ dose and many will not need corticosteroid treatment during pregnancy.

**Environmental Assessment (EA) :**

Tri- Nasal spray qualifies for a tier O environmental assessment. The sponsor should be asked to withdraw EA format items 7, 8, 9, 10, 11 and 15 appendices G, H, I, K and L.

**Recommendation :** The revised labeling and the EA withdrawal request should be conveyed to the sponsor.

5

*/S/*  
Virgil Whitehurst  
Pharmacologist

*July 16, 1996*

CC :

NDA 20,120

HFD-570-/Divfile

HFD-570/HSheevers

HFD-570/WWhitehurst

HFD-570/ASaavedra

HFD-570/ Lng

HFD-571/CSO

HFD-570/MHimmel

*/S/*  
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*7/16/96*

N:\NDA 20-120\pharm\95-04-01.rev

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TABLE B: SUMMARY OF ACUTE TOXICITY STUDIES OF TRIAMCINOLONE ACETONIDE IN MICE AND RATS PREVIOUSLY SUBMITTED IN SUPPORT OF NDAs

Species	Strain	Sex	Route	Weight Range (g)	Vehicle	Dose mg/kg	Observation Period (days)	Report Number <sup>a</sup>	Reference <sup>a</sup>
Mouse	CF-1	F	SC	20-24	0.5% CMC	50, 100	7	18	NDA 19-798 Vol. 2.5, p.242
					0.4% PS-80	200, 400	14		
					0.9% NaCl	800	21		
Rat	Wistar	M	P	90-125	1% Ag. Starch Suspension	6.25, 12.5, 25, 50, 100	7	19	NDA 19-798 Vol. 2.5, p.249
Rat	Wistar	M	IP	90-125	Propylene Glycol	12.5, 18.75, 25, 50	7	20	NDA 19-798 Vol. 2.5, p.260
Rat	Wistar	M	IP	90-125	2% A4 Starch Suspension	6.25, 12.5, 25, 50, 100	7	21	NDA 19-798 Vol. 2.5, p. 272
Rat	Wistar	M	IP	90-125	1% Ag. Starch Suspension	12.5, 25, 50, 100	7	22	NDA 19-798 Vol. 2.5, p.283
Rat	Sherman	M	SC	81 ± 6	0.5% CMC	6, 12, 30	7	23	NDA 19-798 Vol. 2.5, p.295
					0.4% PS-80	60, 120	14		
					0.9% NaCl		21		

a) Reference to location in NDAs 18-117 (December 30, 1977) and 19-798 (December 22, 1988), that have been previously submitted and approved.

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TABLE C: SUMMARY OF MULTIDOSE TOXICITY/CARCINOGENICITY STUDIES PREVIOUSLY SUBMITTED IN SUPPORT OF NDAs

Species	Strain	Initial Group	Mode of Administ.	Doses mg/kg/day	Duration (weeks)	Laboratory	Report No.	Submission Reference <sup>1</sup>
Mouse	Sw/CitCD-1(ICR)BR	16M + 16F	Gavage	2.5, 10, 30	13	—	DS 88-121	ND 7Aug89
	Sw/CitCD-1(ICR)BR	65M + 65F	Gavage	0.1, 0.6, 3	104	—	DS 89-007	DA 19-798, 9Mar93
Rat	Sherman	6M	Diet	100, 300, 900	1	—	25	DA 19-798 Vol. 2.5, 339
	Sherman	6M + 6F	Diet	-75, 200, 750	4	—	29, 30	DA 19-798 Vol. 2.6, 57, 90
	Sprague-Dawley	15M + 15F	Gavage	2.5, 10, 30	13	—	68 (DS 87-055)	DA 19-798 Vol. 2.11, 1
	Sprague-Dawley	60M + 60F	Gavage	0.05, 0.2, 1	104	—	DS 88-006	DA 18-117, 21May92
	Sherman	6M	Subcutaneous	-100, 300, 800, 1700, 3300	1	—	24, 25	DA 19-798 Vol. 2.5, 305, 339
	Sprague-Dawley	3M + 3F	Subcutaneous	500, 2500, 5000	3	—	28	DA 19-798 Vol. 2.5, 357
	Sprague-Dawley	10M + 10F	Subcutaneous	40, 120, 400	10	—	27, 28	DA 19-798 Vol. 2.6, 1, 37
	Sprague-Dawley	5M + 5F	Inhalation	80, 400, 800	5	—	31, 32	DA 19-798 Vol. 2.6, 122, 154
	Sprague-Dawley	10M + 10F	Inhalation	80, 400, 800	10	—	33	DA 19-798 Vol. 2.6, 196
	Sprague-Dawley	5F	Inhalation	40, 120, 400	28 <sup>a</sup>	—	34	DA 19-798 Vol. 2.6, 258
	Sprague-Dawley	10M + 10 F	Inhalation	5 (daily): 20, 60, 180 (4 days/week)	28 <sup>a</sup>	—	35, 36	DA 19-798 Vol. 2.6, 264, 360
	Rabbit	New Zealand White	6M + 6F	Subcutaneous	200	13	—	37, 38
Dog	Beagle	1M	Oral (Capsule)	2000	8	—	39	DA 19-798 Vol. 2.7, 34

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TABLE D: SUMMARY OF REPRODUCTION TOXICITY STUDIES PREVIOUSLY SUBMITTED IN SUPPORT OF NDAs

Species	Study Type	Strain	Initial Group	Mode of Admin.	Doses mg/kg/day	Laboratory	Report No.	Submission Reference <sup>a</sup>
Rat	Segment I	Sprague-Dawley	48, 30, 30, 45 <sup>b</sup>	Gavage	1, 5, 15	—	88 DS 87-084	NDA 18-798 Vol. 2.10, 1
	Segment II	Sprague-Dawley	25	Subcutaneous	1500	—	82	NDA 18-798 Vol. 2.8, 300
Rat	Segment II	Sprague-Dawley	28	Subcutaneous	40	—	53	NDA 18-798 Vol. 2.8, 1
	Segment II	Sprague-Dawley	20	Inhalation	20, 40, 80	—	83	NDA 18-798 Vol. 2.9, 1
	Segment II	Sprague-Dawley	20	Inhalation	20, 40, 80	—	83	NDA 18-798 Vol. 2.9, 1
Rabbit	Segment II	New Zealand White	L: 18; M: 19	Topical (Skin)	20, 100	—	54	NDA 18-798 Vol. 2.8, 48
	Segment II	New Zealand White		Subcutaneous	40, 400, 1800	—	56, 58	NDA 18-798 Vol. 2.9, 117, 140
	Segment II (Range-Finding)	New Zealand White	3F	Inhalation	20, 40, 100, 400, 1800	—	56	NDA 18-798 Vol. 2.9, 117
	Segment II	New Zealand White	12	Inhalation	20, 40, 80	—	56, 57	NDA 18-798 Vol. 2.9, 140, 142
Rat	Segment III	Sprague Dawley	25F	Gavage	0.5, 2.5, 8	—	87 DS 88-001	NDA 18-798 Vol. 2.11, 200

a) Fifteen extra animals per sex in the control group were mated with 15 extra high-dose animals per sex to investigate possible sex-specific effects.

b) Reference to location in NDAs 18-117 (December 30, 1977) and 18-798 (December 22, 1988) that have been previously submitted and approved.

Reference to location in NDAs 18-117 (December 30, 1977) and 18-798 (December 22, 1988) that have been previously submitted and approved.

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The mouse and rat carcinogenic studies for triamcinolone acetate submitted in 1992 and 1993, as part of the phase IV commitment for NDA 18,117. In the conversion of \_\_\_\_\_ to Nasacort AQ, the sponsor decided that a 4 week intranasal study in the dog (to obtain some PK data) and an irritation study in the eye were the only preclinical studies that would be needed as part of the NDA development. As part of this pharmacology review, the 4 week intranasal study in the dog, the irritation study in the rabbit and the carcinogenic studies in the rat and the mouse will be reviewed.

## Subchronic Toxicology 4 Week Intranasal Study in the Dog

(Study # DS- 93-061 carried out by sponsor)

Date Study Initiation : July 23, 1993

Date of Study Completion : April 22, 1994

GLP Statement : Satisfactory

**Methods :**

Beagle dogs ( 5 M & 5 F in the control and high dose groups ; 3 M & 3 F in the low and mid dose groups) were treated intranasally with Nasacort AQ ( RG 5029Y) twice daily for 28 days. The doses were separated by 4 hours. Doses used were 0, 22,44 and 88 mcg/kg (5-20 x the recommended clinical dose on a mcg/kg basis or approximately 3-14 x the recommended clinical dose on a mg/m<sup>2</sup> basis).

Two dogs /sex in the control and high dose were kept for a 2 week reversibility study.

**Parameters Evaluated**

Mortality- daily

Clinical Signs- daily

Body weight- weekly

Food Consumption -daily

Ophthalmology-pretest, weeks 2 and 4

Electrocardiograms -pretest and week 4 (using leads I, II,III, aVR, aVL and aVF)

Toxicokinetics Determinations- days 1 and 28 at 1, 2,4,5, 6,8,10 and 12 after the 1st dose.

Hematology-pretest and week 4

Blood Chemistry- pretest and week 4

Urinalysis-pretest and week 4

Organ Weights-termination

Gross and Histopathology-termination

**Results :**

**Mortality :**

There were no mortalities during the study.

**Clinical Symptoms :**

There were no compound-related clinical signs during the study.

**Body Weight :**

Body weight changes were unremarkable.

**Food Consumption :**

Food consumption changes were unremarkable.

**Ophthalmology :**

There were no indication of compound-related ocular changes.

**Electrocardiograms :**

There were no indication of compound-related EKG changes.

**Toxicokinetic Determinations :**

$C_{max}$  usually occurred at 1 hour postdosing. Drug did not seem to accumulate during the study. The toxicokinetic parameters are given below per the sponsor ( Page 318, Volume 1.8) :

**Nominal Dose (mcg/dog/day)**

Sex	Toxicokinetic Parameter	Day 1			Day 28		
		220	440	880	220	440	880
Male	$C_{max1}$ (ng/ml)	0.35	0.62	1.26	0.36	0.53	0.72
	$T_{max1}$ (hr)	1.0	1.0	1.0	1.0	1.0	1.0
	$C_{max2}$ (ng/ml)	0.47	0.69	1.28	0.64	0.89	0.96
	$T_{max2}$ (hr)	5.3	5.0	5.0	5.0	5.0	5.2
	AUC 0-4hr (ng-hr/ml)	0.70	1.23	2.28	0.87	1.23	2.04
	AUC 0-12hr (ng-hr/ml)	2.05	3.52	5.90	3.15	3.66	5.84
Female	$C_{max1}$ (ng/ml)	0.33	0.85	1.36	0.45	0.43	1.15
	$T_{max1}$ (hr)	2.0	1.0	1.2	1.0	1.2	1.7
	$C_{max2}$ (ng/ml)	0.58	1.60	2.54	0.74	1.02	1.49
	$T_{max2}$ (hr)	5.0	5.0	5.2	5.0	5.0	5.0
	AUC 0-4hr (ng-hr/ml)	0.86	1.85	3.23	0.90	1.05	3.15
	AUC 0-12hr (ng-hr/ml)	2.65	5.75	10.26	3.27	3.97	8.70

These data suggest that there is increased systemic exposure with increasing intranasal dosing. The AUCs do not indicate linear absorption and there were

no meaningful differences between the PK data of males and females.

**Hematology :**

There were no significant changes in the hematology parameters due to Nasacort AQ.

**Blood Chemistry :**

There were no significant changes in blood chemistries due to Nasacort AQ.

**Urinalysis :**

Urine findings were unremarkable.

**Organ Weights :**

Treatment-related changes were observed in the thymus, spleen, adrenals and the liver.

There was a 29-67 % decrease in mean absolute and relative thymus weight in all drug treated groups, however, there was not a clear dose relationship. The decreased thymus weights did correlated with the gross and microscopic findings.

There was approximately an 17-35 % ( not drug-related) decrease in mean absolute and relative adrenal weights. In the mid and high dose dogs, these decreases correlated with gross and microscopic findings.

There was an approximately 30 % increase in the liver weights of the dogs in the high dose group and the liver changes were accompanied by the microscopic observations of increased glycogen accumulation in the hepatocytes.

Mean absolute and relative weight of the spleens in the mid and the high dose groups were greater by approximately 67-103% than the controls, however, these differences were not statistically significant.

**Gross and Microscopic Histopathology :**

Treatment-related effects in the lymphoid organs were characterized by atrophy of the thymus, lymph nodes, spleen and mucosal-associated lymphoid tissue in the ileum and the nasopharynx. Thymic atrophy were noted in 4/6, 4/6 and 6/6 dogs in the low, mid and high dose groups, respectively.

Treatment-related atrophy of the gut-associated lymphoid tissue (GALT) was characterized by the decrease in the number and/or prominence of germinal centers. These changes were observed in 1/5, ( only 5 in this dose group evaluated microscopically), 2/6 and 5/6 dogs in the low, mid and high dose groups , respectively.

Atrophy was also observed in the spleen and the mesenteric and medial retropharyngeal lymph nodes of the dogs in the 44 ( 2/6) and 88 mcg/kg (4/6) groups. Atrophy was associated with a decrease in the number and province of the germinal centers as well as a cortical thickness in some of the lymph nodes.

Test article effects in the adrenal glands were characterized by atrophy and increased vacuolization of the adrenal cortex. Atrophy was also present in the zona fasciculate and the reticularis while increased vacuolation were found in both of these zones as well as the zona glomerulosa. These changes were noted in the low (1/6), mid (4/6) and the high (6/6) dose group. These changes were attributed to the negative feedback inhibition associated with exogenous steroid administration.

Glycogen accumulation (cytoplasmic clearing and vacuolation) was observed in the hepatocytes of 1/6 dogs in the mid dose and 6/6 dogs in the high dose group. These changes are associated with the steroid stimulated effect on CHO metabolism and correlated with increased liver weights.

An increase in the stromal fat was observed in the sternum of one female dog (1/6) in the high dose group. Steroids are known to cause deposition of fat stores.

Listed below are the pathology summary of the one month intranasal study in the dog per the sponsor :

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Microscopic Finding	Males Control	0.022 mcg/kg	0.044 mcg/kg	0.088 mcg/kg	Female Control	0.022 mcg/kg	0.044 mcg/kg	0.088 mcg/kg
Thymus: Minimal-to-mild atrophy	0/3	1/3	3/3	3/3	0/3	2/3	1/1	3/3
Mesenteric associated lymphoid tissue								
Atrophy-Ileum <sup>2</sup>	0/3	0/3	1/3	3/3	0/3	1/3	1/3	3/3
Nasopharynx <sup>3</sup>								
Spleen: Lymphoid atrophy <sup>4</sup>	0/3	0/3	0/3	3/3	0/3	0/3	1/3	0/3
Lymph node (mesenteric): Lymphoid atrophy	0/3	0/3	1/3	1/3	0/3	0/3	1/3	3/3
Adrenal cortex: T vascularization	0/3	1/3	1/3	3/3	0/3	0/3	3/3	3/3
Atrophy	0/3	0/3	1/3	3/3	0/3	0/3	1/3	1/3
Liver: T glycogen	0/3	0/3	0/3	3/3	0/3	0/3	1/3	1/3
Spleen (mesenteric): T arterial cell	0/3	0/3	0/3	0/3	0/3	0/3	0/3	1/3

1) Findings at end of dosing period. Effects at all dose levels showed evidence of reversibility after a 14-day recovery period.  
 2) Minimal-to-moderate severity  
 3) Tendency for lymphoid aggregates of nasopharynx to decrease from mild to minimal

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## Recovery Period Dogs :

Treatment related atrophy were still evident in the thymus, mesenteric lymph node, spleen and the GALT of 2/6 dogs in the high dose group. For all other adverse events, there was evidence of reversibility although not completely. A recovery period was not carried out for the mid and low dose groups.

NOAEL : Less than 22 mcg/kg

## Summary of the 4 Weeks Intranasal Study :

A 4 week intranasal study was carried out in the dog. The doses used were 22, 44 and 88 mcg/kg. These doses induced lymphoid associated toxicity in the thymus, spleen, liver, adrenal glands, gut and the nasopharynx as well as the lymph nodes. These treatment-related changes were initiated at AUCs of approximately 0.78 ng.hr/mL in the dogs while healthy male volunteers

administered a single intranasal dose of 240 mcg of Nasacort had AUCs of approximately 0.10 ng.hr/mL . There was no clearly defined NOAEL in this study, particularly for the nasopharynx and gut associated lymphoid tissues as well as the atrophy of the thymus.

In a 2 week recovery period, it was disclosed that the treatment- related effects on the liver, gut , adrenals and thymus were not completely reversible.

There were several shortcomings in this study : (1) this study was not really long enough to determine the subchronic/chronic effects of Nasacort AQ on the nasal mucosa, (local toxicity), the study should have been at least 6 months since it is unclear how long the drug will be used. Additionally, the local toxicity of this steroid probably should be determined in an appropriate animal model since we know that steroids can adversely effect lymphoid associated tissues in the nose and the pharynx. ; (2) there was no special means to determine microleakage ( Evans Blue dye) or cellular infiltration/inflammation in the nasal mucosa/tissues . The sponsor should have attempted to determine the effect of Nasacort AQ on abraded or a wound/sore in the nasal tissues; (3) further, the sponsor should have utilized naso and bronchoalveolar lavage to appraise any early epithelial changes in the nasal and pulmonary tissues including cellular population changes as well as changes in mediators and enzymes ; (4) The NOAEL for the gut and nasopharynx associated lymphoid associated tissues was not established..

The sponsor recommends that the drug be used only for 3 weeks consecutively.

And finally, it was not stated when the EKGs were carried out. EKGs should be carried out at  $C_{max}$  if possible.

## Special Study

### Ocular Irritation Study in the Rabbit

Study Number DS 93-064

Study was carried out by Rhone-Poulenc Rorer Central Research

Date Initiation : July 9, 1993  
Date Completion : February 16, 1994  
GLP Statement : Satisfactory

**Methods :**

Three male white rabbits ( approximately 3 months old) were used. A single application of Nasacort AQ (0.1 ml) was placed into the interior conjunctival sac of the right eye of each rabbit. The conjunctival, iris and cornea were examined for irritation at 1, 24 and 48 hours. Lesions were examined using the Draize scale.

**Results :**

Nasacort AQ was found to be irritating at the 1 hour examinations. The eye was unclouded (no irritation) at the 24 and 48 hour examinations.

**Summary of the Special Study :**

A 0.1 ml of Nasacort AQ was introduced into the conjunctival sac of rabbits and the eyes were examined at 1, 24 and 48 hours. Nasacort AQ was found to be irritating 1 hour after dosing. After 24 hours, no irritation was observed.

**Carcinogenic Studies :**

Oral Carcinogenicity Study of Triamcinolone Acetonide in the Albino Mouse (Volume 1.8-1.9 of NDA 19,798).

Project # 83715

Study was carried out by \_\_\_\_\_

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GLP statement : Satisfactory

Date Initiation : September 8, 1989  
Date completion : January 25, 1993.  
Carcinogenicity Mouse Study was submitted to NDA 19-798 on March 9, 1993.

**Methods :**

Triamcinolone acetonide (Lots # 8709069 and # 8908087) dissolved in distilled water was given orally by gavage to mice (Mus musculus), Swiss CrI :CD<sup>R</sup> -1(ICR)BR strain, (approximately 28 days old) for 104 weeks. There was 65 males and 63 females in each dose group, and the doses were :

<u>Dose Groups</u>	<u>Doses</u>
1)vehicle control	distilled water (weeks 0-46), deionized water (weeks 47-104)
2)vehicle control	distilled water(weeks 0-46), deionized water (weeks 47-104)
3)triamcinolone	0.1 mcg/kg
4)triamcinolone	0.6 mcg/kg
5)triamcinolone	3.0 mcg/kg

The drug dose volume was 10 ml/kg/day and given 7 days per week. The dose selection was based on the results of a 13 weeks dose-finding study (study # 83831). The high dose was selected based on decrease in body weight gain, approximately 10% as well as hepatocellular vacuolization and thymus lymphocytolysis in the mice dosed at a dose of 10 mcg/kg. These effects were not observed in the mice dosed at 2.5 mcg/kg (per telephone conversation with the sponsor during the week of September 18-21, 1995) .

Drug plasma level of the test article was evaluated on weeks 16 and 56.

**Parameters Evaluated :**

Mortality : twice daily

Clinical Signs : daily for the first 22 weeks, then weekly

Body weights : pretreatment and then weekly

Food Consumption : pretreatment and then weekly

Ophthalmoscopy : pretreatment, months 12, 18 and 24

Drug Plasma Levels : pretreatment, weeks 16 and 56 using radiolabeled triamcinolone acetonide.

Laboratory Chemistries : pretreatment and terminal

Urinalyses :pretreatment and terminal

Organ Weights: terminal  
 Gross Pathology : terminal  
 Histopathology : terminal

## Results :

### Mortality :

<u>Group</u>	<u>Males</u>		<u>Females</u>	
	<u>Mortality</u>	<u>%Survival</u>	<u>Mortality</u>	<u>%Survival</u>
1)Vehicle	27/50	46	33/50	34
2)Vehicle	33/50	34	26/50	48
3)0.1 mcg/kg	36/65	45	35/65	46
4)0.6 mcg/kg	34/64	47	37/65	43
5)3.0 mcg/kg	37/65	43	41/65	38

The were no meaningful differences between males and females or between the controls and the treated animals.

The major cause of death in this study was amyloidosis (accumulation of insoluble fibrillar proteins in various organs and tissues), the second cause of deaths was genitourinary and inflammatory skin lesions in males and lymphoma in females. Additionally, there were 30 deaths (21 males and 9 females) due to handling during gavage procedures.

### Clinical Signs :

The most common clinical signs were abdominal distension and blue skin coloration., weakness, reduced activity, reduced body temperature, abnormal respiration and tremors. The clinical sign were not drug-related.

Cutaneous and subcutaneous masses were similar among all groups, treated and controls.

### Body Weight :

There was no meaningful decreases in body weight gain in the treated mice in this study. During weeks 0-82, there was approximately a 8-10 %decrease in

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body weight gain in the females in the high dose group. However, by the end of the study, 104 weeks, the body weight gains were similar in the females in the high dose group. Body weight gains for this study are listed below as presented by the sponsor (Volume 18.1, page 43):

GROUP 1 VEHICLE CONTROL GROUP 2 VEHICLE CONTROL GROUP 3 TRIAMCINOLONE ACETONIDE 0.1 MC/KG/DAY					GROUP 4 TRIAMCINOLONE ACETONIDE 0.6 MC/KG/DAY GROUP 5 TRIAMCINOLONE ACETONIDE 3.0 MC/KG/DAY					
MALES					SEX	FEMALES				
1	2	3	4	5	GROUP	1	2	3	4	5
					WEEK 0-26					
9.62	10.05	10.04	9.32	9.69	MEAN	7.83	7.74	8.22	7.50	7.45
2.264	2.894	2.024	2.588	2.280	± S.D.	1.785	1.720	2.221	1.691	2.243
					WEEK 26-52					
2.10	1.42	2.02	1.96	1.86	MEAN	2.61	2.51	2.17	1.85 A	2.50
1.226	1.898	1.204	1.153	1.487	± S.D.	1.975	1.792	2.076	1.370	1.461
					WEEK 53-78					
0.40	-0.94	0.13	0.09	-0.26	MEAN	1.13	0.42	1.14	1.54	0.74
1.760	2.211	1.474	1.653	1.750	± S.D.	2.147	2.357	1.859	2.803	2.100
					WEEK 79-104					
-1.14	0.16	-0.31	0.16	-0.71	MEAN	0.72	1.91	2.55	1.46	1.86
3.465	1.201	2.907	1.142	2.374	± S.D.	2.691	3.311	3.407	2.988	2.636

\* CALCULATED AS THE MEAN OF THE INDIVIDUAL BODY WEIGHT GAINS OF RATS SURVIVING TO THE END OF THE PERIOD.  
SIGNIFICANTLY DIFFERENT FROM CONTROL (COMBINED GROUP 1 AND 2) VALUES: A - P < .05 (DUNNETT'S).

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### Food Consumption :

The food consumption was not affected by treatment with triamcinolone acetonide at doses up to 3.0 mcg/kg for 104 weeks. The food consumption was comparable for treated as well as control mice.

### Ophthalmoscopy :

The results of these examinations reveal no treatment -related ocular changes due to the test article. Central corneal opacities and /or various types of cortical cataracts were observed, however, these findings were observed in each dose group and were considered incidental in origin and were not

treatment related.

### Hematology :

There were no significant differences observed in the hematology parameters when comparing the treated and the control mice.

### Drug Plasma Levels :

This was a single dose evaluation in which the drug plasma levels were determined 1 hour after dosing. Radiolabeled triamcinolone acetonide [6,7,<sup>3</sup>H(N)] was given by gavage at levels 0, 0.1, 0.6 and 3.0 mcg/kg. One hour later, the animals were sacrificed and the drug plasma level, defined as the percentage of the dose present in the total plasma of the animal at termination, was calculated using textbook values for plasma volumes based on body weight.

Overall,  $1.2\% \pm 0.25$  of the dose administered appeared in the plasma 1 hour after dosing and the drug plasma level data suggests a linear dose response. However, a one point bioavailability measurement is probably not adequate to determine bioavailability or linear dose response. The mean dose administered, the mean plasma concentration and the mean % of the dose are summarized below :

<u>Group</u>	<u>Week</u>	<u>Mean Dose</u> <u>µg/kg</u>	<u>Mean Dose</u> <u>pg/ml</u>	<u>Mean %</u> <u>Dose in plasma</u>
0.1*	16	0.118	27.18	1.1±0.13
	56	0.096	24.79	1.2±0.31
0.6*	16	2.451	613.2	1.2±0.13
	56	0.596	168.0	1.3±0.27
3.0*	16	3.070	664.0	1.0±0.22
	56	2.988	694.0	1.1±0.32

\* Triamcinolone acetonide

Pharmacokinetic data (PK) would be much more beneficial than drug plasma levels. PK data should have included  $T^{max}$ ,  $C^{max}$  AUCs, half lives and whether there were any metabolites(active metabolite ?), whether the drug really does

have linear pharmacokinetics and how the drug is handled and eliminated.

Laboratory Chemistries : Laboratory Chemistries were similar when drug treated mice were compared to control mice.

Urinalyses : Urinalyses were unremarkable for all mice in this study.

Organ Weights : There were no significant organ weight changes .

Gross Pathology : No gross findings which could be associated with the oral administration of triamcinolone acetonide were seen in any of the mice examined. The tumors observed grossly were typical of those commonly observed in control CD-1 mice in long term studies.

### Histopathology :

Neoplasms Findings : The total number of primary neoplasms disorders among the treated groups were comparable to those observed in the controls. Microscopic examinations revealed a slight, but statistical significant , increase in lymphomas in the females in the high dose group, the incidence of lymphomas in the high dose females is comparable with the incidence in controls in a recent 2 year carcinogenicity study in CD-1 at

—————The incidence of Systemic Lymphomas are summarized below :

### Incidence of Systemic Lymphoma

<u>SEX</u>	<u>FEMALES</u>					
	1	2	1+2	3	4	5
Group						
Dose(mcg/kg)	0	0	0	0.1	0.6	3.0
# in Group	50	50	100	65	65	65
Lymphoma	3	7	10	11	11	13*
Lesion(%)	(6)	(14)	(10)	(17)	(17)	(20)

\* Significant at  $p > 0.05$  level

A slightly greater number of bronchoalveolar tumors (combined adenoma and carcinoma) for the treated males was observed but lacked significance in comparison to the controls in the trend test.

The incidence of combined benign and malignant tumors was significantly different ( $p < 0.05$ ) in the high dose males when compared with the control males in the Fisher's test. However, this finding is considered to reflect biologic variation observed with a common spontaneous tumor in CD-1 mice. The incidence of bronchoalveolar adenoma and carcinoma are shown below per the sponsor :

INCIDENCE OF BRONCHOALVEOLAR ADENOMA & CARCINOMA

Sex	<u>MALE</u>						<u>Trend Test</u> <u>P-Value</u>
Group	1	2	1+2	3	4	5	
Dose (ug/kg/day)	0.0	0.0	0.0	0.1	0.6	3.0	
No. In Group	50	50	100	64	64	65	
<b>Lesion (Z)</b>							
<b>Lung:</b>							
BRONCHOALVEOLAR ADENOMA	14 (28.0)	10 (20.0)	24 (24.0)	22 (34.4)	21 (32.8)	23 (35.4)	0.128
BRONCHOALVEOLAR CARCINOMA	5 (10.0)	2 (4.0)	7 (7.0)	10 (15.6)	1 (1.6)	7 (10.8)	0.443
BRONCH. ADENOMA & CARCINOMA	19 (38)	12 (24)	31 (31.0)	28 (44.0)	22 (34.4)	30* (46.2)	0.052

\* Significantly different ( $p < 0.05$ ) from control via Fisher's test

The most frequent neoplasms in this study were found in the lung, liver,

hemopoietic system and Harderian gland( finding were not significant). Pulmonary tumors (bronchoalveolar adenoma and bronchoalveolar carcinoma) were observed in all groups in both sexes as single and multiple tumors located in both subpleural and peribronchial location. The tumors consisted of continuous cords of uniform cuboidal cells lining alveolar sets and occasionally expanding into alveolar spaces to form compact masses.

**Non-Neoplastic Findings :** There were no non- neoplastic findings which were considered to have a relationship to treatment with triamcinolone acetate at the doses utilized.

Treatment of Swiss mice with oral doses of triamcinolone acetate up to 3.0 µg/kg for a minimum of 104 weeks revealed no evidence of carcinogenicity.

### Oral Carcinogenicity Study of Triamcinolone Acetate in the Albino Rat (Volume 18.1-18.6 of NDA 18-117)

Carried out by \_\_\_\_\_ Project # 83200

GLP statement : Satisfactory

Date study Initiated : October 13, 1988

Date Study completion : November 11, 1990

Carcinogenicity study in the rat were submitted to NDA 18-117 on May 21, 1992.

#### Methods :

Sprague-Dawley rats (CrI:CD<sup>R</sup>(SD)BR strain, 60/sex were included per dose group. Triamcinolone acetate (lots — # 8709069 and 8908087) was distilled in water and gavaged daily for 104 weeks. The dose groups were :

<u>Group/Treatment</u>	<u>Doses</u>
1) vehicle Control	Distill water
2) vehicle Control	Deionized Water
3) triamcinolone acetate	0.05 mcg/kg

- |                          |            |
|--------------------------|------------|
| 4) triamcinolone acetate | 0.2 mcg/kg |
| 5) triamcinolone acetate | 1.0 mcg/kg |

Additionally, 10 rats/sex were assigned to each group and used for the measurement of drug plasma levels (there were no pharmacokinetic studies).

Dose selection for this carcinogenic study was based on a 10 week subchronic dose finding study. Inhalation doses ( nose only), 80, 400 and 800  $\mu\text{g}/\text{kg}$  induced dose-related weight loss and muscle wasting. Also observed were drug related increases in creatinine, SGOT and potassium levels as well as decreased BUNs and calciums. Hematological changes observed were drug-related lymphopenia, eosinopenia and neutrophilia. Additionally, increased excretion of electrolytes chloride, potassium, sodium and inorganic phosphate. Drug related decreases (significant) were found in the spleen and the thymus in the high dose group. Histological findings included lymphoid depletion of the spleen and lymph nodes and adrenal cortical atrophy.

#### Parameters Evaluated :

Mortality : twice daily

Clinical Signs : daily for the first 4 weeks and then weekly thereafter

Body Weights : weekly

Ophthalmoscopy : pretreatment and week 104

Laboratory Investigations : pretreatment and terminal

Urinalyses : pretreatment and terminal

Drug Plasma Levels : weeks 18 and 59

Organ Weights : terminal

Gross Pathology : terminal

Histopathology : terminal

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## Results :

### Mortality :

The mortalities were distributed as follows :

<u>Group</u>	<u>Males Survival</u>		<u>Females Survival</u>	
1) Vehicle Control	39/60	35%	33/60	45%
2) Vehicle control	46/60	23%	38/60	37%
3) Triamcinolone: 0.05µg/kg	44/60	27%	34/60	43%
4) Triamcinolone: 0.2 µg/kg	44/60	27%	39/60	35%
5) Triamcinolone: 1.0 µg/kg	42/60	30%	41/60	32%

The distribution of the mortalities showed no evidence of a treatment-related difference. There was insufficient survival in all the control and drug-treated rats in this study. A large number of deaths occurred during weeks 84-104. During week 84, survival rates were as follows :

<u>Group</u>	<u>Males</u>	<u>Females</u>
1)control	80%	77%
2)control	77%	78%
3)0.05 µg/kg	57%	77%
4)0.02 µg/kg	65%	73%
5)1.0 µg/kg	73%	75%

During the final 20 weeks of the study, the percentage survival in the high dose group dropped from 73% to 30 % in males and 75% to 32 % in females. These data suggest that the deaths maybe age related rather than a drug related effect.

The major cause of death in the rats included pituitary adenoma, glomerulonephropathy as well as mammary carcinoma in the females.

### Clinical Signs :

Clinical signs included areas of thinning of the fur, staining of the fur in various body regions, areas of scabs formation, skin lesions and/ulceration of the tail, limbs and masses. However, these were not drug-related.

### Body Weights :

Body weight gains were comparable among all control and treatment groups except for the high dose females. In the high dose females, body weight gain decreases were approximately 12 %. The group mean body weight gains are shown below per the sponsor (volume 18.1, page A 1):

GROUP 1 VEHICLE CONTROL		GROUP 3 TRIAMCINOLONE ACETONIDE 0.25 UC/KG/DAY			GROUP 5 TRIAMCINOLONE ACETONIDE 1.0 UC/KG/DAY					
GROUP 2 VEHICLE CONTROL		GROUP 4 TRIAMCINOLONE ACETONIDE 0.2 UC/KG/DAY								
MALES					SEX	FEMALES				
1	2	3	4	5	GROUP	1	2	3	4	5
					WEEK					
					0-26					
443.7	456.0	465.8	459.2	447.6	MEAN	199.7	214.5	190.8	209.0	195.7
64.12	65.16	63.27	73.09	69.51	± S.D.	34.61	44.14	52.12	49.76	35.22
					WEEK					
					26-52					
100.8	104.0	99.7	107.8	105.6	MEAN	95.6	93.7	96.9	106.0	106.0
46.47	46.11	41.97	39.80	46.65	± S.D.	31.65	42.44	44.73	43.80	39.62
					WEEK					
					52-78					
16.1	34.1	23.2	30.7	5.1	MEAN	62.3	76.3	50.8	54.0	57.5
111.45	63.74	90.96	81.48	115.37	± S.D.	63.62	48.14	79.39	58.12	68.00
					WEEK					
					78-104					
-112.2	-34.9	-123.5	-72.1	-86.5	MEAN	12.7	28.1	3.3	33.3	-34.8
146.02	114.50	139.48	122.06	112.49	± S.D.	83.34	98.21	87.04	68.89	144.02

\* CALCULATED AS THE MEAN OF THE INDIVIDUAL BODY WEIGHT GAINS OF RATS SURVIVING TO THE END OF THE PERIOD.

These data show that the doses of triamcinolone had no effect on body weight gain in the males and nor the females in the low and mid dose groups. The data suggest that the MTD was not utilized in this study.

### Food Consumption :

Food consumption was comparable among all control and treated rats. Total food intake for male and female rats was essentially the same as the total food intake in the control rats.

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### Ophthalmoscopy :

There were no treatment-related eye changes that were attributed to the test agent in this study.

### Hematology :

There was no significant differences between the hematology parameters in the treated rats when compared with the parameters in the control rats.

### Drug Plasma Level :

The drug plasma levels of orally dosed <sup>3</sup>H-labeled triamcinolone were determined during weeks 18 and 59. These determinations made 1 hour after dosing show that the drug plasma levels were approximately linearly proportional to the administered dose. The drug plasma levels were similar between sexes. At the highest dose of 1.0 mcg/kg, the mean plasma concentration of triamcinolone was 769±174 pg.eg/mL ( sexes and study weeks combined).

The mean plasma levels for week 18 were 40.9, 180 and 819 pg.eq/mL and for week 59 were 31.7, 135 and 712 pg.eq/mL for doses 0.05, 0.2 and 1.0 mcg/kg.

**Urinalyses :** Urinalyses were comparable in treated and control rats.

**Gross Pathology :** No gross finding were observed that could be attributable to the oral administration of triamcinolone acetoneide.

**Histopathology : Neoplasm Findings :**Microscopic evaluations revealed an increase in total proliferative adrenal medullary lesions in the high dose females consisting of both focal medullary hyperplasia and pheochromocytoma. These findings were thought to be fortuitous. Additionally, there was 2 other neoplasms, pituitary adenoma in both sexes and Zymbal's gland tumor in males observed in this study. However, there was no relationship between the test article and these neoplasms and therefore,

these findings were considered to be incidental.

**Non- Neoplasms :** There were no increases in the incidence of non-neoplastic findings that were considered to be treatment-related.

In conclusion, oral doses of triamcinolone acetonide up to 1  $\mu\text{g}/\text{kg}$  administered to Sprague- Dawley rats for 104 weeks did not induce carcinogenicity.

### Summary of the Carcinogenic Studies :

**Mouse Study :** Triamcinolone acetonide dissolved in water was administered by gavage to mice at daily doses of 0.1, 0.6 and 3.0  $\mu\text{g}/\text{kg}$  for 104 weeks. The basis for the selection of this study was a 13 weeks dose ranging study in which microscopic changes in the liver and thymus as well as a 10 % decrease in body weight gain was observed in the 10  $\mu\text{g}/\text{kg}$  dose group.

At the oral doses used, which were probably below the MTD, ( the high dose maybe 1/3 of the MTD), there was minimal effect on the body weight gain in the triamcinolone treated mice. All doses used in this study were below the recommended clinical dose of 4.4  $\mu\text{g}/\text{kg}$ .

Results of this study reveal a slight, but statistical significant increase in lymphomas in the high dose females. However, the incidence of lymphomas was comparable with the incidence of lymphomas observed in the controls in a recent carcinogenicity study carried out by the sponsor.

There was an increase in bronchoalveolar tumors, not significant, in the triamcinolone treated male mice as well as significant differences in the incidence of combined benign and malignant tumors in the high dose male mice. However, the tumors in the drug treated groups were not biological significantly different from tumors in the control group.

**Rat Study :** Oral doses of 0.05, 0.2 and 1.0  $\mu\text{g}/\text{kg}$  were gavaged daily to Sprague-Dawley rats for 104 weeks. The bases for the selection of these doses

were a 10 week inhalation dose ranging study ( inhalation doses 0, 80, 400 and 800  $\mu\text{g}/\text{kg}$  in which all dosed groups exhibited toxic effects). The number of surviving rats in this study was less than 25 out of 60/ sex in each dose group. However, there ~~was~~<sup>were</sup> sufficient survivors (73%) at week 84.

Additionally, the MTD was probably not utilized . However, triamcinolone at the high dose ( 1.0 $\mu\text{g}/\text{kg}$ - approximately 3.0% of the recommended clinical dose on a  $\mu\text{g}/\text{m}_2$  basis) induced <sup>no effects but</sup> a slight decrease in body weight gain of approximately 12 % in the high dose females, however, no other toxic effects were reported . Body weight gain changes were not observed in the high dose males.

In the rat studies, pituitary and adrenal medullary tumors were increased in the treated rats. However, these findings were not significant.

Acceptability of the phase IV carcinogenic studies with regard to the use of the MTD will depend on the recommendations of the CAC.

### Overall Summary :

Nasacort AQ is intranasal spray (triamcinolone acetone- active agent) which is to be used for the treatment of seasonal and perennial allergic rhinitis. The recommended daily clinical dose is 220 mcg or 4.4 mcg/kg for a 50 kg person. In some cases, a higher dose maybe prescribed (440 mcg or 8.8 mcg/kg) The sponsor is recommending that this drug be used for 3 weeks only.

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There are 2 approved NDAs for triamcinolone acetone, clinical data from these NDAs reveal that systemic corticosteroids are known to adversely affect non-target organs at therapeutic doses if given over a sufficient period. These untoward effects include hypothalamic-pituitary-adrenal( HPA) axis, immunosuppression, enhanced bone resorption( osteoporosis), alterations in CHO metabolism and CNS-mediated behavioral disturbances. Clinical trials with Nasacort AQ revealed that the most common adverse events were

pharyngitis, rhinitis, headache and epistaxis.

Human pharmacokinetic studies comparing different triamcinolone acetonide containing formulations show that the AUC of Nasacort AQ is approximately 2.8 times higher than that of Nasacort CFC. Since chronic Nasacort AQ administration results in greater human exposure than Nasacort CFC, there is the potential for more severe toxicities (local and systemic), particularly in the elderly. The potential for added toxicity should be investigated in a chronic animal study.

The summary below compares the human pharmacokinetics of different triamcinolone acetate containing formulations ( submitted by sponsor ) :

The following compares the Pharmacokinetics of different Triamcinolone Acetonide-containing formulations:

TA Product	Age	Dose ( $\mu\text{g}/\text{day}$ )	$C_{\text{max}}$ (ng/mL)	AUC (ng X hr/mL)
Nasacort-CFC	18-46	440	0.21	1.36 (0-12 hr)
	18-50		0.16	1.70 (0- $\infty$ )
_____	18-46		0.20	1.31 (0-12 hr)
Nasacort-AQ	18-50		0.82	4.68 (0- $\infty$ )
Azmacort-CFC	20-44	600	1.33	8.88 (0-24 hr)
			_____	1.61

*COMMENT: AUC of Nasacort AQ is approximately 2.8 times higher than that of Nasacort CFC. Systemic exposure to Azmacort-CFC at 600  $\mu\text{g}$  (maximum recommended dose is 1200  $\mu\text{g}/\text{day}$ ) is approximately twice that of 440  $\mu\text{g}$  Nasacort AQ.*

These data confirm higher human AUCs (0- $\infty$ ) with Nasacort AQ, 4.68 ng X hr/hr compare with Nasacort CFC (0- $\infty$ ) 1.70 ng X hr.

Since the toxicological profile for triamcinolone has been extensively studied in human and animals only 2 preclinical studies were submitted for this NDA. The major preclinical study is a 4 week investigation in the dog. Intranasal doses in this studies of 22, 44 and 88 mcg/kg caused treatment-related atrophy of the adrenals and the thymus, lymphoid associated gut, nasopharynx

and ileum. The NOAEL for triamcinolone was not clearly delineated in this study. However, this study did reveal a typical steroid, treatment-related atrophy of the adrenals, thymus and lymphoid associated gut, nasopharynx and ileum was initiated at approximately 0.78 ng.hr/mL.

Additionally, the local toxicity of triamcinolone ( toxicity of the nasopharynx tissues) was not delineated in the dog study. There were no special analyses or dyes employed to resolve whether triamcinolone provokes microleakage of the nasal tissues, changes in cellular population, inflammatory/irritation responses or the drug effect on abraded or injured ( impaired) tissues. Further, there was no attempt to correlate drug plasma levels with drug effects.

A re-review of the previous summary of preclinical studies reveal 4 inhalation studies in the rat ( duration 5-26 weeks), 1 intranasal study in the dog ( 4 weeks) and 1 inhalation study in the monkey ( 76 weeks).

In the rat studies, Nasacort AQ final formulation was not used and in the 26 weeks studies, the drug was given intermittently ( 4 days a week). In the 5 and 10 weeks studies, \_\_\_\_\_ was administered. There were no PK data in these studies.

In the monkey study, the drug was given as a MDI only 4 days per week for the first 42 weeks, then daily for the last 34 weeks. Nasacort AQ final formulation was not used and there were no PK data.

The 4 week intranasal study in the dog deminstrated typical steroid-like effects. No local toxicity was reported.

The carcinogenic potential of triamcinolone acetonide was probably not adequately addressed in the carcinogenic studies because the MTD was not employed in either studies. There were no body weight changes in the mouse study and limited body weight changes in the females in the rat study. Additionally, there were no scientific basis for the dose selection used in these studies. Furthermore, local carcinogenic potential in the nasal cavity by the

proposed route has not been investigated.

Mutagenicity studies with triamcinolone acetonide have not been carried out.

The reproduction, impairment of fertility and teratogenicity of triamcinolone acetonide were adequately addressed in the repro/tox studies. Triamcinolone acetonide was teratogenic in rats and rabbits (inhalation doses up to 80  $\mu\text{g}/\text{kg}$ ) and monkeys (inhalation dose of 500  $\mu\text{g}/\text{kg}$ ). No impairment of fertility was reported in rats administered oral doses up to 15  $\text{mg}/\text{kg}$ . However, triamcinolone acetonide at an oral dose of 5.0  $\text{mg}/\text{kg}$  and higher caused dystocia, prolonged delivery, increases in fetal resorptions and stillbirths as well as decreases in pups body weight and survival.

In general, the types of toxicities and the target organs observed with triamcinolone acetonide are similar regardless of the route of administration (target organs-adrenals, liver, thymus and spleen). However, triamcinolone acetonide has the potential to induce bacterial infections, suppurative inflammatory reactions, lymphopenia. These adverse events are probably caused by the immunosuppression effects of triamcinolone. The potential for bacterial infections and/or inflammatory reactions are enhanced by greater systemic exposure and chronic applications.

Listed below are preclinical nose only inhalation and intranasal studies previously and currently submitted by the sponsor and reviewed: (data from sponsor)

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## SUMMARY OF TRIAMCINOLONE ACETONIDE MULTIDOSE STUDIES WITH NASAL EXPOSURE SUBMITTED TO FDA

Species	Group Size	Mode of Administration	Dose (ug/kg/day)	Duration (weeks)	Laboratory	Report No.	Submission Reference
Rat	5M + 5F	Nose only Inhalation, TAA	80, 400, 800	5	—	31, 32	NDA 19-798 Vol. 2.6, 122, 154
Rat	10M + 10F	Nose only Inhalation, TAA	80, 400, 800	10	—	33	NDA 19-798 Vol. 2.6, 194
Rat	5F	Nose only Inhalation, MDI	40, 120, 400	28 <sup>a</sup>	—	34	NDA 19-798 Vol. 2.6, 258
Rat	10M + 10 F	Nose only Inhalation MDI	5 (daily); 80, 80, 180 (4 days/week)	28 <sup>b</sup>	—	35, 36	NDA 19-798 Vol. 2.6, 268, 360
Dog	L.M: 3M + 3F C.H: 6M + 5F	Intranasal with clinical Nasacort AQ formulation & apparatus	20, 40, 80	4	—	DS 90-0e1	NDA 20-488 Vol. 8, 66
Monkey	L.M: 2M + 2F H: 4M + 4F	Inhalation, MDI	20 <sup>c</sup> , 60 <sup>c</sup> , 180 <sup>d</sup>	76	—	50, 51	NDA 19-798 Vol. 2.8, 1, 79

<sup>a</sup> Intranasal treatment.

<sup>b</sup> Daily throughout the study.

<sup>c</sup> 4 consecutive days of dosing per week for the first 41 weeks of study; intranasal daily. Increased dose to 120 ug/kg/day from week 42 to end of study.

<sup>d</sup> 4 consecutive days of dosing per week for the first 41 weeks of study; intranasal daily. Increased dose to 360 ug/kg/day from week 42 to end of study.

<sup>e</sup> Low-dose group, Medium-dose group, Control group, High-dose group

<sup>f</sup> NDA 19-798 submitted 23-Dec-88

<sup>g</sup> NDA 20-488 submitted 29-Jun-94

After re-reviewing the inhalation and intranasal toxicity studies for triamcinolone acetonide and discussing these data with Dr Joe Sun, acting supervisory pharmacologist, it was agreed that an additional chronic intranasal toxicity studies is not necessary. We agreed that the 76 weeks inhalational study in the monkey was adequate to support the recommended 3 weeks and/ clinical use of triamcinolone intranasally. We are aware that the inhalation study in the monkey does not meet the scientific standards of 1995. The drug was only given 4 days/week for the first 42 weeks, then daily for the next 34 weeks, there were no drug plasma levels or PK data included and administration was via inhalation rather than intranasally. However, lung and tracheal tissues were examined by electron microscopy.

Furthermore, Nasacort CFC has been approved previously and all the inactive ingredients in the AQ formulation are commonly used in other

Pregnancy :

Pregnancy Category C. Triamcinolone acetate \_\_\_\_\_  
\_\_\_\_\_ f 20, 40 and 80 mcg/kg in rats (approximately  
\_\_\_\_\_ times the recommended clinical dose on a mcg/m<sup>2</sup>  
basis, respectively) and rabbits ( approximately \_\_\_\_\_ times the  
recommended \_\_\_\_\_ dose on a mcg/m<sup>2</sup> basis, respectively). \_\_\_\_\_

\_\_\_\_\_ Dose- related  
teratogenic effects in rats and rabbits included cleft palate \_\_\_\_\_ internal  
hydrocephaly and axial skeletal defects \_\_\_\_\_

\_\_\_\_\_ There are no  
adequate and well controlled studies in pregnant women. Triamcinolone  
acetate should be used during pregnancy only if the potential benefit  
justifies the potential risk to the fetus.

Recommendation :

NDA is approvable. Acceptability of the phase IV carcinogenicity studies  
will depend on the recommendations of the CAC. The labeling should be  
revised as recommended.

IS/ \_\_\_\_\_  
Virgil Whitehurst 9/26/95  
Pharmacologist

- CC
- NDA-HFD/155/div file
- NDA-HFD/155/JSUN
- NDA-HFD/155/VEW
- NDA-HFD/155/BRogers
- NDA-HFD-155/MedOfficer
- NDA-HFD/155/CSO/S Barner

IS/ \_\_\_\_\_  
Sept. 26, 1995

APPEARS THIS WAY  
ON ORIGINAL