

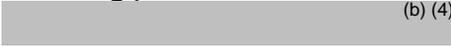
**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22382Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**Final Version**  
**(August 13, 2009)**  
**Clinical Pharmacology Review**

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<b>NDA: 22-382</b>	<b>Dates of Submission:</b> December 5, 2008
<b>Generic Name</b>	Ketorolac Tromethamine
<b>Brand Name:</b>	<b>SPRIX®</b>
<b>Formulation:</b>	Solution
<b>Strengths:</b>	15.75 mg per actuation  (b) (4)
<b>OCP Division</b>	Division of Clinical Pharmacology II
<b>OND Division</b>	Division of Anesthesia, Analgesia, and Rheumatology Products
<b>Route of Administration:</b>	Nasal
<b>Proposed Indication:</b>	Moderate to Severe Pain that requires analgesia at the opioid level
<b>Dosage and Administration:</b>	<ul style="list-style-type: none"><li>• Adults (&lt;65 years): 31.5 mg (2 sprays, 15.75 mg spray in each nostril) Q6-8 h X 5 days (max 126 mg per day)</li><li>• &gt;65 years, renally impaired, and &lt;50 Kg (110 lbs): 1 spray (15.75 mg) Q6-8 h (max 63 mg per day).</li><li>• Pediatrics: SPRIX has not been shown to be safe and effective in pediatric patients</li></ul>
<b>Type of Submission:</b>	New Formulation and Route of Administration
<b>Sponsor:</b>	Roxro Pharmaceuticals (Menlo Park, CA)
<b>Reviewer:</b>	Sayed (Sam) Al Habet, R.Ph., Ph.D.
<b>Team Leader</b>	Suresh Doddapaneni, Ph.D.

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## 1.0 Executive Summary

### 1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable provided that a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant.

### 1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no phase 4 commitment is applicable to this NDA.

### 1.3 Summary of Important Clinical Pharmacology Findings:

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). It is a potent analgesic that inhibits cyclooxygenase (COX). The drug was first approved in the United States in 1989 under the trade name Toradol® for intravenous (IV) and intramuscular (IM) injection (NDA 19-698). Subsequently, in 1991 oral Toradol® formulation was approved (NDA 19-645).

Based on the current approved label, the drug is indicated for short-term management of moderately severe, acute pain following surgical procedures in adults over 17 years of age. The total duration of treatment utilizing the oral and/or intramuscular route of administration is **not to exceed 5 days**. The drug is not indicated in pediatric population. The sponsor is not seeking a pediatric indication and has requested a deferral from conducting pediatric studies in this NDA.

This is the **first** ketorolac nasal spray solution with similar dosing regimen as that of Toradol® (i.e., Q4-6 h or Q6-8 h PRN for a maximum duration of 5 days). Since the sponsor obtained the right of reference to Toradol® NDAs this submission was considered under 505(b)1 regulation. From a clinical pharmacology perspective, the sponsor labeling is based on the currently approved label for special populations such as renal and hepatic impairment with specific information related to absorption and distribution for this route.

The sponsor's primary goal in the development of this product is to achieve blood level within the range of that obtained following the commonly used 15 mg and 30 mg IM doses in clinics.

In this NDA, the sponsor submitted 11 clinical pharmacology studies and 4 safety and efficacy studies. The clinical pharmacology studies were conducted to characterize the PK of intranasal ketorolac primarily in healthy subjects and one drug interaction study in subjects suffering from allergic rhinitis. The safety and efficacy studies were conducted in patients with post-operative pain. Therefore, the clinical pharmacology studies will be

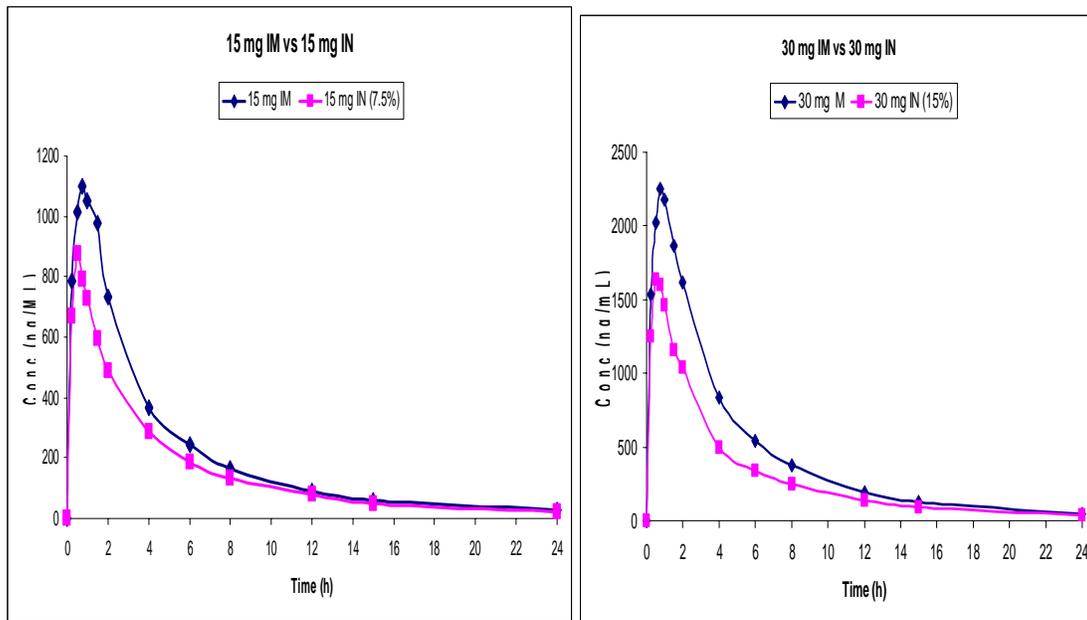
considered supportive (not primary) to the safety and efficacy data generated from the clinical trial studies for the approval of this new formulation.

This is a solution formulation containing 15% ketorolac (157.5 mg/mL), edetate disodium (b) (4) monobasic potassium phosphate (b) (4) sodium hydroxide (pH 7.2), and sterile water for injection (q.s). It should be noted that, in the early developmental studies, the sponsor tested solutions of different ketorolac concentrations ranging from 1.5% to 22.5% (b) (4). However, all subsequent clinical pharmacology studies and Phase III studies used the final-to-be marketed formulation containing 15% ketorolac (b) (4).

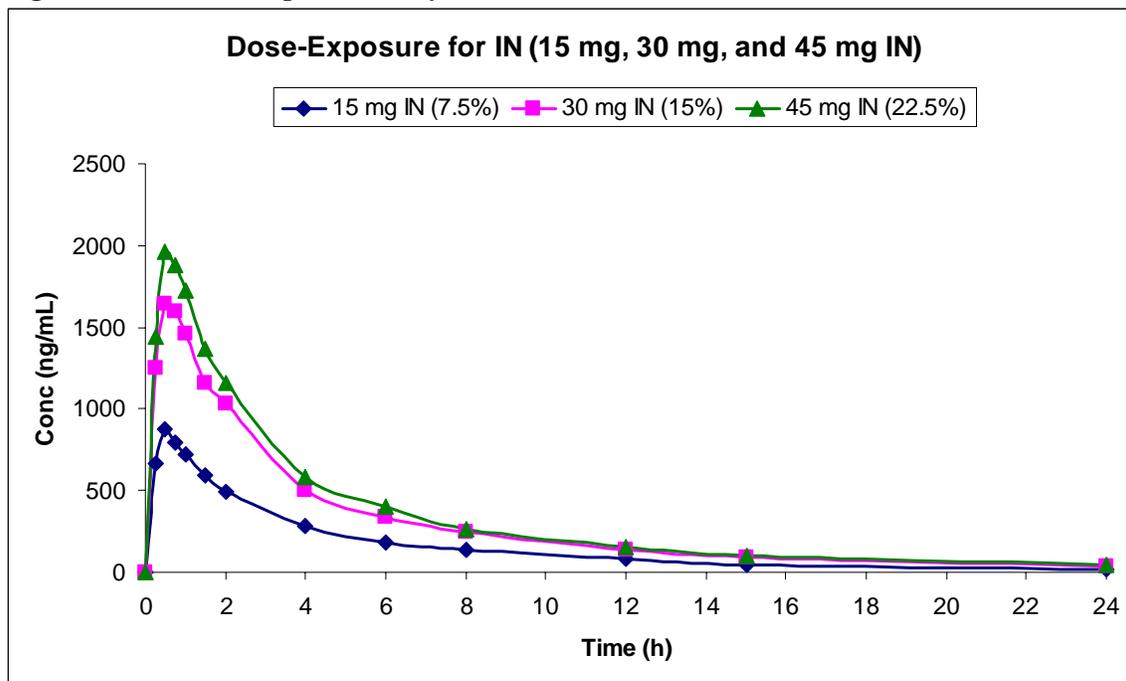
From all clinical pharmacology studies, it can be concluded that ketorolac is sufficiently absorbed following intranasal administration (**Figure 1 A & B**). The C<sub>max</sub> occurs within 30-60 min similar to the IM administration. The steady state was achieved within 24 hours after multiple dose administration at a dosing regimen of Q6 h and Q8h for 3 days or 5 days (**Studies ROX-2001-03 and ROX-2005-03**).

**Figure 1 A and B. Mean of Ketorolac Plasma Concentration-Time Profiles After Intramuscular (IM) Administration of 15 mg and 30 mg and Intranasal (IN) Administration of 15.5 mg, 31.5 mg, and 48 mg (Study # ROX-2001-002)**

**Figure 1 A. Intramuscular (IM) vs. Intranasal (IN)**



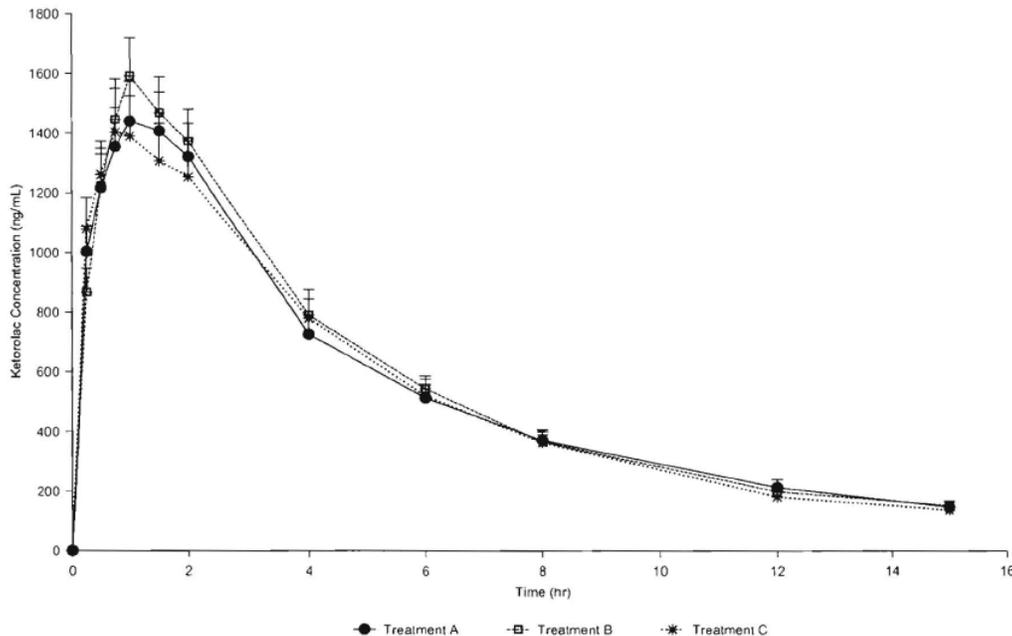
**Figure 1 B. Dose Proportionality for Intranasal Administration**



The plasma level after intranasal ketorolac appears to be within the level obtained after IM administration of 15 mg and 30 mg (**Study # ROX 2001-02**) with none of the studies showing bioequivalence between the intranasal and IM or IV administration (**Studies # ROX 2001-02 and 1993-01**). The bioavailability of intranasal ketorolac relative to IM was approximately 73% at 15 mg dose and 60% at 30 mg dose (**Study # ROX 2001-02**). From a different study and at the same dose of 30 mg, the absolute bioavailability (relative to IV) of intranasal ketorolac at 30 mg dose was also approximately 60% (**Study # ROX 1993-01**). It should be noted that IN 30 mg dose was tested with 15% solution concentrations and is the relevant concentration for the proposed product.

There was no evidence of effect of commonly used intranasal preparations such as oxymetazoline (OTC Afrin® in US) and fluticasone propionate (Rx Flonase® in US) on the absorption of intranasal ketorolac when administered concurrently in healthy subjects or in patients with allergic rhinitis (**Figure 2, Studies ROX-2007-03 and ROX 2006-03, and ROX 2006-04**).

**Figure 2 Mean ( $\pm$  SE) Plasma Concentration-Time Profiles When Administered Alone or with Oxymetazoline or Fluticasone in patients with Allergic Rhinitis (Study # ROX-2007-03)**



The PK appears to be comparable in elderly (>65 years of age) and nonelderly (<65 years of age) (Study ROX-2007-02). The C<sub>max</sub> and AUC appear to be slightly higher by ~10% and 23% in elderly compared to nonelderly, respectively. The magnitude of increase in exposure in elderly does not directly warrant dose adjustment, unless there are other accompanied reasons such as renal insufficiency in elderly.

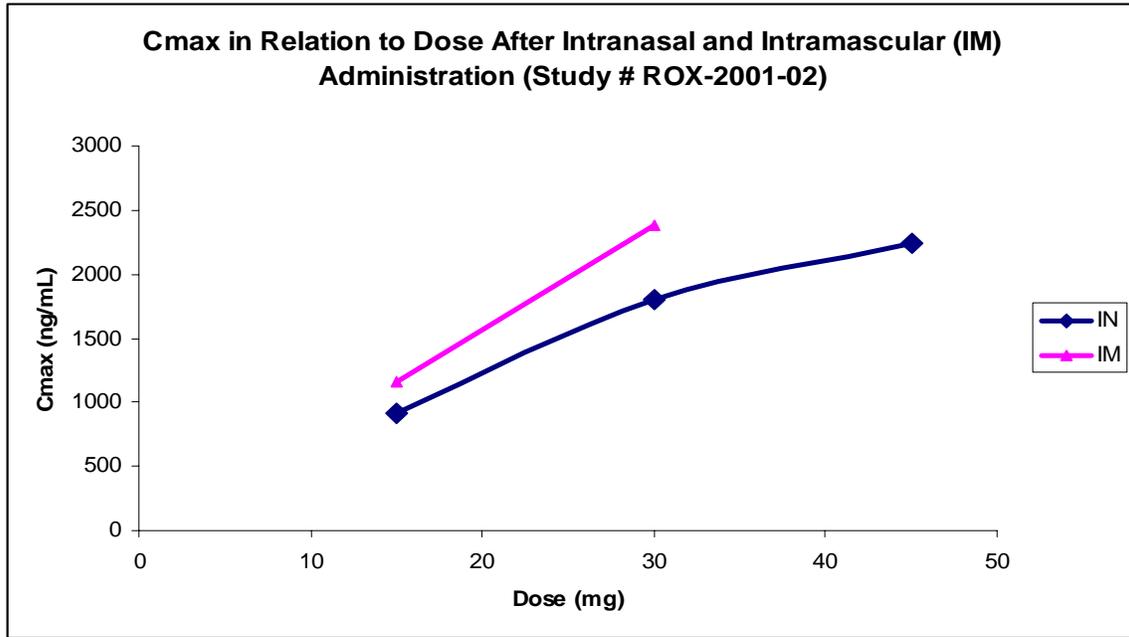
Currently, approved ketorolac products are not indicated for use in pediatrics. Sponsor is requesting a deferral of pediatric studies at this time. The IN product is delivered via a metered dose pump, calibrated to deliver a predefined dose appropriate for adult use only.

(b) (4)

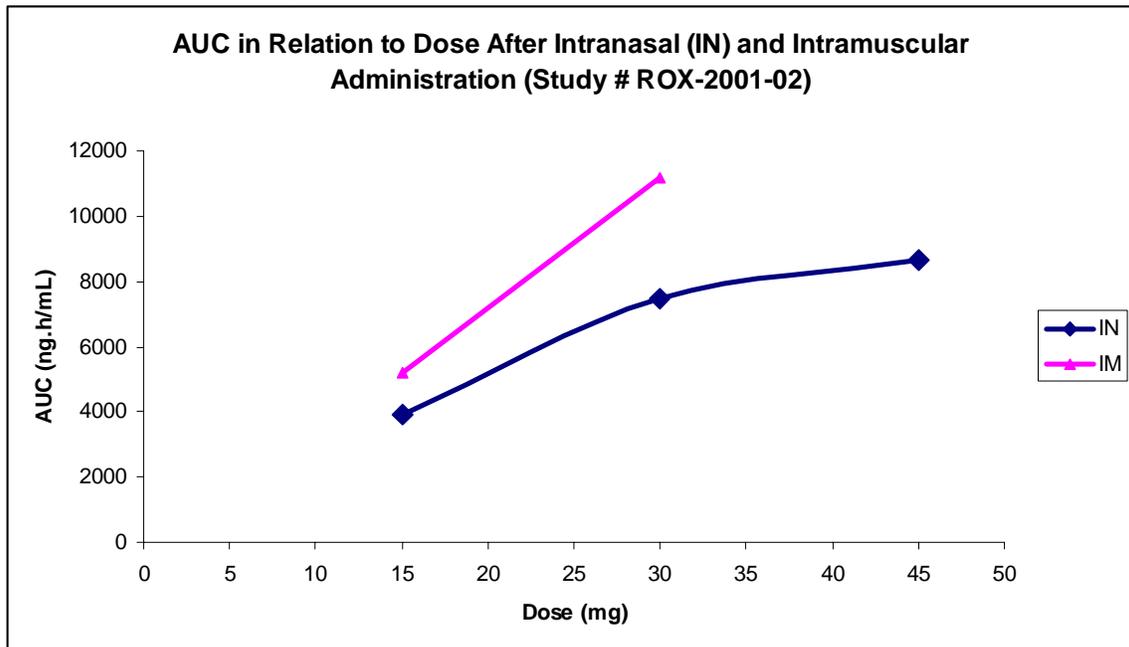
However, due to the fact that elderly patients are more sensitive to ketorolac side effects (GI tract AEs) and carry a lower recommended dose (half the young adult dose) for the IM ketorolac product, the sponsor proposed a reduced dose of 15 mg Q6h-8 hours in elderly >65 years of age. This is acceptable. In case of children under 17 years of age, the sponsor is not seeking an indication for use in pediatric patients at this time.

From all studies conducted in this NDA, although there was increase in exposure with dose, there was a consistent trend for less than proportional increase in exposure at doses greater than 30 mg (Figures 3 and 4).

**Figure 3. Mean of Ketorolac Cmax After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**

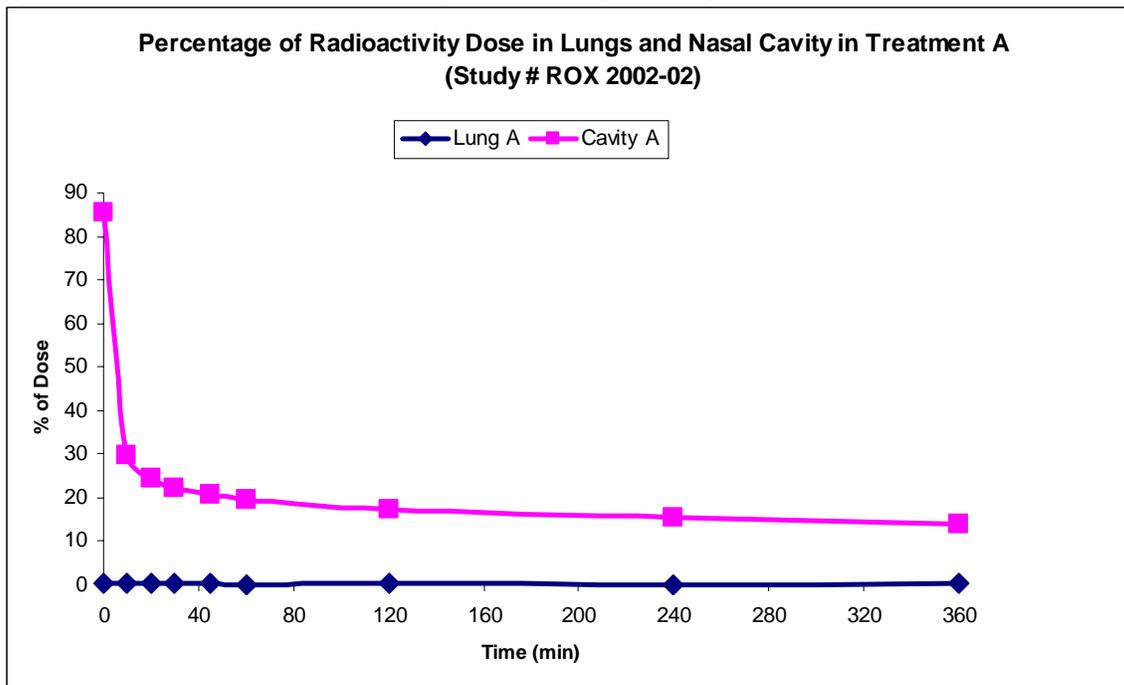


**Figure 4. Mean of Ketorolac AUC<sub>(0-inf)</sub> After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**



In terms of the local/site distribution of the solution (droplets) after intranasal administration, the radiolabeled ( $^{99m}\text{Tc}$ ) drug appears to mainly reside in the nasal cavity (~70% to 85%) with a negligible percentage in lungs (<0.5%).

**Figure 5. 1. Mean Delivered % of Dose in Lungs and Nasal Cavity in Treatment A (gentle sniff-inhalation with subject standing) (Study # ROX-2002-02)**



**Conclusions:**

It can be concluded that the intranasal administration of 30 mg ketorolac provides a substitution to the IM or IV administration by achieving blood levels within 15 mg to 30 mg doses of IM route.

Since the plasma level after intranasal administration is within that obtained after IM administration of 15 mg and 30 mg doses, no specific dose adjustment is necessary with the intranasal route in special populations apart from that already indicated in the currently approved labeling for other ketorolac preparations. In addition, the systemic safety with intranasal ketorolac should not be any worse than the intramuscular route as the blood level after 30 mg dose is consistently lower (rather than higher) after the IM administration.

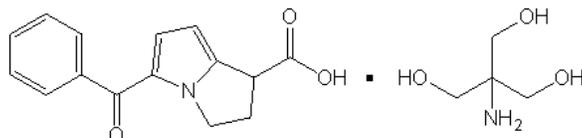
Overall, the NDA is acceptable from a clinical pharmacology perspective.

## 2. Question Based Review

### 2.1 General Attributes/Background:

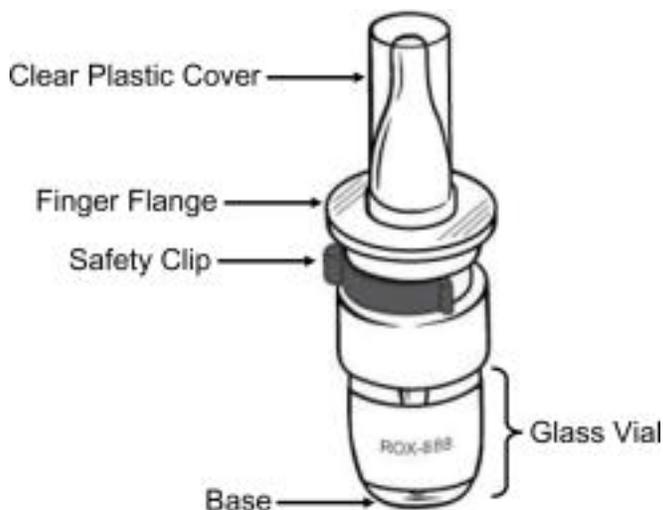
#### 2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The drug is highly soluble in water (b) (4). The molecular weight is 376.41. Its structural formula is as follows:



The sponsor developed spray solution for nasal administration (**Figure 2.1.1.1**). It is 15% (b) (4) solution filled in a multidose Type I clear glass bottle attached with a metered/dose pump to deliver 100  $\mu$ L (15.75 mg) volume (**Table 2.1.1.1**). The nominal fill weight is 1.7 gram/bottle, which is equivalent to approximately (b) (4) of the solution. The unit is intended to deliver a maximum 8 actuations per day. Each actuation (100  $\mu$ L) will deliver 15.75 mg dose of ketorolac per nostril. In this case, each dose is 31.5 mg (2 x 15.75 mg). The unit must be discarded within 24 hours of its first use (see CMC review for details). According to the sponsor, the limitation of 8 actuations per unit would minimize overdosing and drug abuse potential.

**Figure 2.1.1.1. Scheme of Spray Unit/Bottle.**



**Table 2.1.1.1. Composition of Nasal Spray Drug Product Solution**

Table 2.3.P.1-1. Drug Product Unit Composition							
Ingredient	mg/spray <sup>a</sup>	Amount			mg/bottle <sup>c</sup>		Function
		(b) (b) ( )	(b) (b) <sup>b</sup> ( )	(b) % ( )	8 sprays	(b) (4)	
Drug Substance:					(b) (4)		
Ketorolac Tromethamine USP	15.75	(b)	(b)	(b)			Active ingredient
Excipients:		( )	( )	( )			
Edetate Disodium USP	(b)	(b)	(b)	(b)			(b) (4)
Monobasic Potassium Phosphate (b)	(b)	(b)	(b)	(b)			(b)
Sodium Hydroxide (b)	pH 7.0	(b)	(b)	(b)			pH adjustment
(b) (4) water for Injection USP	q.s. ad	(b)	(b)	(b)			(b) (4)
Total	105	(b)	(b)	(b)			
<sup>a</sup> Based on a nominal spray of 100 µL (=105 mg) per actuation.							(b) (4)

It should be noted that the product identifier (code) used by the sponsor in some documents, tables, and figure throughout the NDA is “**ROX-888**”. This code represents the proposed standard dose of 31.5 mg which consists of two 100 µL sprays of 15% w/w solution of ketorolac tromethamine.



**2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?**

**2.1.2.1 Mechanism of Action:**

Ketorolac tromethamine is a potent analgesic nonsteroidal anti-inflammatory drug (NSAID) that inhibits the enzyme cyclooxygenase (COX 1 and 2) in the arachidonic acid cascade. This results in the reduction in the syntheses of the inflammatory mediators such as prostaglandins, thromboxanes, and prostacyclin. Like most of the other NSAIDs, it possesses anti-inflammatory, analgesic, and anti-pyretic effects.

Ketorolac, like other NSAIDs, can cause peptic ulcers, gastrointestinal bleeding and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Due to its high potency and related side effects (see below), the total duration of use of ketorolac by any route (including nasal spray) **should not exceed 5 days**.

Therefore, it is contraindicated by any route (including nasal spray) in patients with peptic ulcer disease and other GI Tract conditions. Elderly patients are at greater risk for serious gastrointestinal events. In addition, the drug is contraindicated in patients with advanced renal impairment or other kidney diseases.

#### 2.1.2.2.2 Proposed Indications:

(b) (4)

#### 2.1.4 What are the Core Studies Submitted in this NDA?

The sponsor conducted a total of 15 studies for the development of the product. These include 11 clinical pharmacology/PK studies and 4 safety and efficacy studies. These studies are briefly outlined below:

##### **Clinical Pharmacology/BE Studies:**

**Study # REC-1993-01:** This was a pilot single dose, crossover study comparing 10 mg and 30 mg intranasal ketorolac to 10 mg IV ketorolac in 12 healthy subjects. Based on this study the absolute bioavailability of ketorolac was 86% and 56 % after 10 mg and 30 mg intranasal doses, respectively. The Cmax occurred between 30 min to 60 min.

**Study # ROX-2001-01:** This was a single dose proportionality study of 20, 30, and 40 mg intranasal administration [REDACTED] (b) (4). An additional arm was included in this study [REDACTED] (b) (4) at a dose of 30 mg. The study showed increase in exposure with increase in dose, but was less than proportional at the highest dose of 40 mg. [REDACTED] (b) (4)

**Study # ROX-2001-02:** This was a dose ranging study at 15, 30, and 45 mg intranasal doses and 15 mg and 30 mg IM doses in 15 healthy subjects. As was the case in study ROX-2001-01, the exposure was dose proportional but was less than proportional at the highest dose of 45 mg. The exposure after 30 mg intranasal dose appears to be within the range of exposure produced after 15 mg and 30 mg IM doses. Based on this data, the sponsor selected 30 mg dose for further development.

**Study # ROX-2001-04:** Based on the finding from study ROX-2001-02, the sponsor conducted multidose study at a dose of 30 mg Q6h for a total of 20 doses in 15 healthy subjects. This study demonstrated that the exposure obtained is within the therapeutic range established after IM administration.

**Study # ROX-2005-03:** This was a multidose PK study at 3 doses per day for 3 days up to 7 total doses in healthy subjects at a dose of 30 mg every 8 hours. At steady state, the exposure was approximately 43% greater than on Day 1 which was within that expected level after IM administration.

**Study # ROX-2007-02:** This is a special population study in elderly and young adults subjects following a single 30 mg intranasal dose. The AUC of ketorolac in elderly appears to be slightly higher by approximately 23% than in young adults.

**Study # ROX-2006-02:** This was a pediatric study in 20 children between ages of 12 to 17 years after single doses of 15 mg and 30 mg intranasal ketorolac. The AUC of ketorolac appears comparable or slightly higher in children compared to adults. According to the sponsor's proposed label, the drug is not indicated in children.

**Study # ROX-2006-03:** This was a drug interaction study with the nasal spray oxymetazoline at ketorolac intranasal dose of 30 mg in healthy subjects. No drug interaction was noted with oxymetazoline.

**Study # ROX-2006-04:** This was another drug interaction study with 30 mg intranasal dose of ketorolac and 200 mcg intranasal multiple doses of fluticasone propionate in healthy subjects. No significant effect on blood level of ketorolac was noted with fluticasone.

**Study # ROX-2007-03:** This was an additional/confirmatory drug interaction study in patients with allergic rhinitis following a single dose of 30mg intranasal ketorolac and a single dose of the nasal spray oxymetazoline and multiple doses (x 5 days) of fluticasone propionate. Based on this study, neither oxymetazoline nor fluticasone showed significant effect on ketorolac exposure after nasal administration.

**Study # ROX-2002-02:** Based on the Agency's recommendation, the sponsor conducted a scintigraphy study using <sup>99m</sup>Tc labeled ketorolac to rule out that the drug is not inhaled and deposited into the lung. Based on the results from this study a negligible amount of the drug was deposited into the lung (<0.5% of dose).

### **Clinical Trial Studies (Phase II and Phase III):**

The sponsor conducted 2 Phase II studies and 2 Phase III studies as briefly summarized below:

**Study # ROX-2001-03:** This was a Phase II double-blind placebo controlled, multiple dose study at a dose of 10 mg TID for 2 days in 85 patients with post-operative pain. No PK samples were collected in this study.

**Study # ROX-2003-05:** This was a Phase II double-blind placebo controlled, single 30 mg dose study in 40 patients with dental pain (n= 40 active and n=40= placebo). No PK samples were collected in this study.

**Study # ROX-2003-01:** This was a Phase III double-blind placebo controlled, multiple dose study in 199 patients with pain following major surgery (n=199 active and n=101 placebo). The drug was administered at 30 mg dose three times daily (TID) up to 5 days. No PK samples were collected in this study.

**Study # ROX-2005-01:** This was a Phase III double-blind placebo controlled, multiple dose study in 214 patients with pain following abdominal surgery (n=214 active and 107 placebo). The drug was administered at a dose of 30 mg four times daily (QID) up to 5 days. No PK samples were collected in this study.

## **2.2 General Clinical Pharmacology**

### **What are the Available Ketorolac Preparations?**

Originally, ketorolac was first approved for IV/IM injection under the brand name Toradol® on November 30, 1989 for Syntex Pharma (currently Roche Pharma) at 15 mg/mL and 30 mg/mL strengths (NDA 19-698). Later, Toradol® 10 mg oral tablet was approved in December 20, 1991 for the same sponsor (NDA 19-645). In 2005, both products (NDA 19-698 injectable Toradol® and NDA 19-645 for oral Toradol®) were discontinued from the market for non safety and non efficacy reasons. It should be noted however that the current sponsor cross referenced both NDAs in the current submission.

Although, the original products were discontinued from the market, other generic products were available at that time and currently still marketed. For example, on April 26, 1999 the two strengths of 15 mg/mL and 30 mg/mL IV/IM injection were approved for Bedford Pharma (ANDAs 75,222 and 75,228).

The drug is also available in ophthalmic preparations. The first ophthalmic preparation was approved in November 9<sup>th</sup>, 1992 as 0.5% solution under the trade name Acular® for Allergan Pharma (b) (4). Subsequently two additional Acular® preparations were approved: one as preservative free at 0.5% solution on November 3, 1997 (NDA 20-811) and another as 0.4% solution in May 30, 2003.

### **What is the Sponsor's Rational for Nasal Spray?**

Based on this long history of use, the clinicians are highly familiar with ketorolac's benefit/risk profile and its maximum 5 days duration of use. Therefore, it has commonly been used for short duration of analgesia in clinics mainly by intramuscular administration.

From the clinical pharmacology perspective, and due to the unique solubility profiles of ketorolac, the sponsor's primary goal in the development of this product is to achieve blood level within the range of that obtained following the commonly used 15 mg and 30 mg IM doses in clinics. An intranasal formulation avoids painful IM/IV injections and/or

oral administration in some nauseated patients. Therefore, the sponsor’s proposed indications are the same as that for IM/IV product with alternative route of administration of ketorolac.

**2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?**

The safety and efficacy of ketorolac (Toradol®) parental and oral preparations are well established since early 1990s. However, no information is available on the safety and efficacy of nasal spray preparation. Therefore, the sponsor conducted four clinical studies to assess the safety and efficacy of the ketorolac nasal spray in patients with postoperative and dental extraction pain scales (Studies # ROX-2001-03, ROX-2003-05, ROX-2003-01, and ROX-2005-03).

In these studies, the efficacy was established based on the following end points:

- Summed Pain Intensity Difference (SPID) as the primary efficacy endpoint. For Phase III trials, the sponsor used 6-hour SPID (SPID6) as the primary efficacy endpoint.
- Pain intensity (PI) as measured on a 100-mm visual analog scale (VAS) with 0 = no pain and 100 = worse pain possible.
- Pain intensity difference (PID) scores were calculated by subtracting the post-treatment PI scores from the baseline score.

Overall, the drug demonstrated efficacy over placebo in patients with post-operative pain (Tables 2.2.1.1 and 2.2.1.2).

**Table 2.2.1.1. Summary of SPID6 Scores (Study ROX-2005-01)**

	<b>ROX-888 n = 213</b>	<b>Placebo n = 107</b>	<b>P-value</b>
Mean (SE)	115.6 (7.98)	92.6 (11.08)	
Median	110.8	99.0	
Range	-179.0 – 429.7	-234.0 – 363.1	
Least square means (SE)	117.4 (7.71)	89.9 (10.59)	0.032 <sup>a</sup>
Difference in means		27.6	
95% CI		2.5 – 52.7	

a. The 2-way ANCOVA with the Day 0 pre-dose PI score as a covariate in the model was used to analyze differences between the 2 treatment groups.

**Table 2.2.1.1. SPID Scores at 6 Hours (Study ROX-2003-01)**

<b>Treatment Group</b>	<b>SPID6</b>
Placebo, mean (SE)	37.2 (12.87)
ROX-888, mean (SE)	83.3 (10.60)

(ANOVA,  $P=0.007$ , Wilcoxon rank-sum,  $P=0.003$ , ANCOVA,  $P=0.006$ ).

In terms of safety, there were no unexpected systemic adverse events that that are commonly observed after oral or IM/IV ketorolac. However, there was noticeable local nasal irritation and discomfort after intranasal administration compared to placebo (**Table 2.2.1.3**). In all listed side effect, the placebo effect was lower than after ketorolac.

<b>Adverse Event, n (%)</b>	<b>IN ketorolac 10 mg (n= 43)</b>	<b>ROX-888 (n= 495)</b>	<b>Placebo (n= 290)</b>	<b>Total (n= 828)</b>
Nausea	25 (58.1%)	256 (51.7%)	149 (51.4%)	430 (51.9%)
Pyrexia	24 (55.8%)	134 (27.1%)	129 (44.5%)	287 (34.7%)
Constipation	8 (18.6%)	127 (25.7%)	82 (28.3%)	217 (26.2%)
Vomiting	12 (27.9%)	119 (24.0%)	65 (22.4%)	196 (23.7%)
Headache	15 (34.9%)	106 (21.4%)	58 (20.0%)	179 (21.6%)
Flatulence	2 (4.7%)	88 (17.8%)	57 (19.7%)	147 (17.8%)
Anemia	12 (27.9%)	80 (16.2%)	37 (12.8%)	129 (15.6%)
Tachycardia	7 (16.3%)	56 (11.3%)	52 (17.9%)	115 (13.9%)
Pruritus	8 (18.6%)	56 (11.3%)	48 (16.6%)	112 (13.5%)
Epistaxis	3 (7.0%)	53 (10.7%)	28 (9.7%)	84 (10.1%)
Nasal discomfort	4 (9.3%)	67 (13.5%)	6 (1.7%)	78 (9.2%)
Hypotension	4 (9.3%)	42 (8.5%)	20 (6.9%)	66 (8.0%)
Dizziness	7 (16.3%)	28 (5.7%)	27 (9.3%)	62 (7.5%)
Rhinalgia	2 (4.7%)	56 (11.3%)	1 (0.3%)	59 (7.1%)
Insomnia	2 (4.7%)	35 (7.1%)	19 (6.6%)	56 (6.8%)
Hypokalemia	5 (11.6%)	20 (4.0%)	18 (6.2%)	43 (5.2%)

In summary, all of the four clinical trails in postoperative and dental pain showed a statistical significant effect compared to placebo. In terms of safety, local nasal irritation and discomfort were reported by some subjects in all studies including some of the clinical pharmacology studies. All other systemic adverse events of the new route are comparable to that of the oral and IM routes. These systemic adverse events are well known since ketorolac availability in 1990s. For final assessment of the safety and efficacy data, refer to the clinical review by Dr. Robert Levin.

## **2.2.2 What are the Characteristics of Drug Metabolism and Disposition?**

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is ( $\pm$ )-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). It exists in a racemic mixture of [-]S and [+]R.

The drug is mainly metabolized by hydroxylation and then undergoes conjugation with glucuronic acid. The renal route is the primary route of excretion of the parent drug and its metabolites with approximately 92% of the dose excreted in urine (~40% as metabolite and 60% as unchanged ketorolac). Approximately 6% of a dose is excreted in the feces.

The drug is highly bound to plasma proteins (~99.2%). It does not appear that ketorolac induces or inhibits hepatic enzymes responsible for its own metabolism or other drugs.

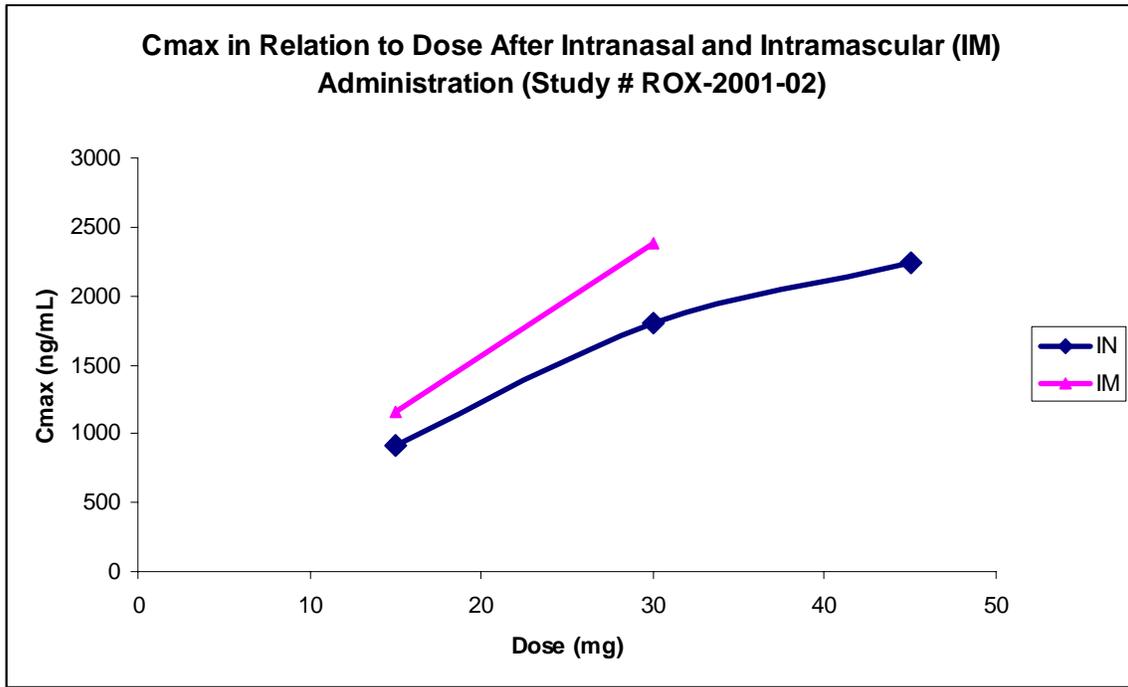
Specific study was conducted to determine the potential deposition of the drug in the lung after intranasal administration using scintigraphy technology (Study # ROX-2002-02).

## **2.2.3 Dose-Proportionality**

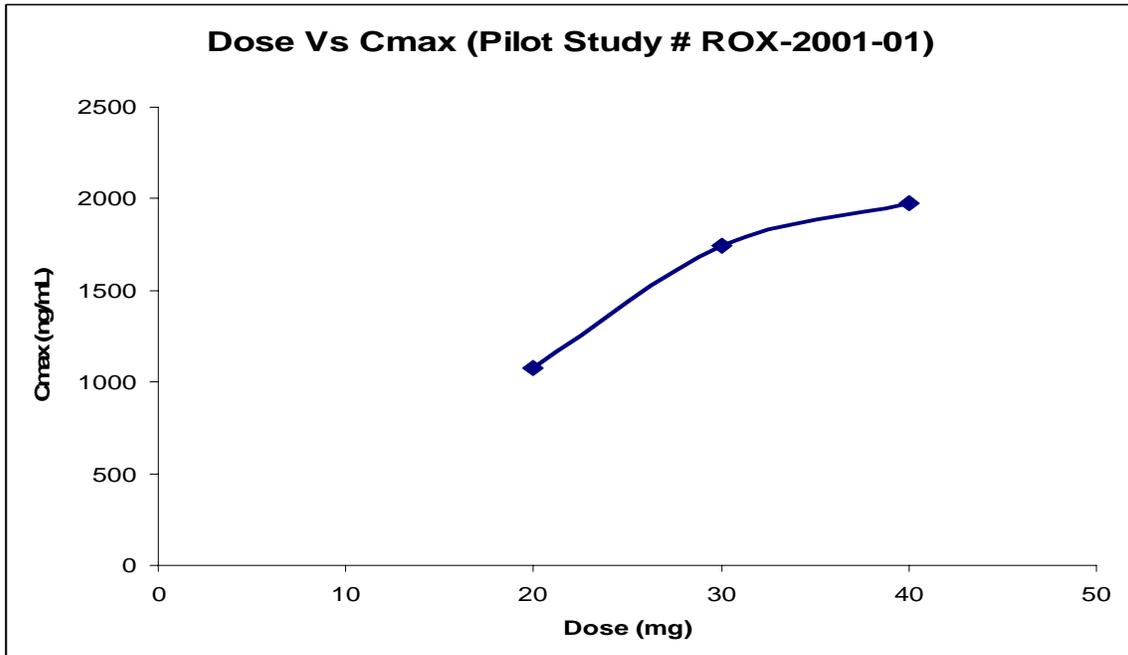
### **2.2.3.1 What are the characteristics of the dose-systemic exposure relationships?**

The sponsor conducted two studies to determine the exposure level in relation to the nasal dose (Studies ROX-2001-01 and ROX-2001-02). Both studies demonstrated lack of dose proportionality at a dose greater than 30 mg for both C<sub>max</sub> although there was an increase in exposure with dose (**Figures 2.2.3.1 and 2.2.3.1**) and AUC (**Figures 2.2.3.3 and 2.2.3.4**).

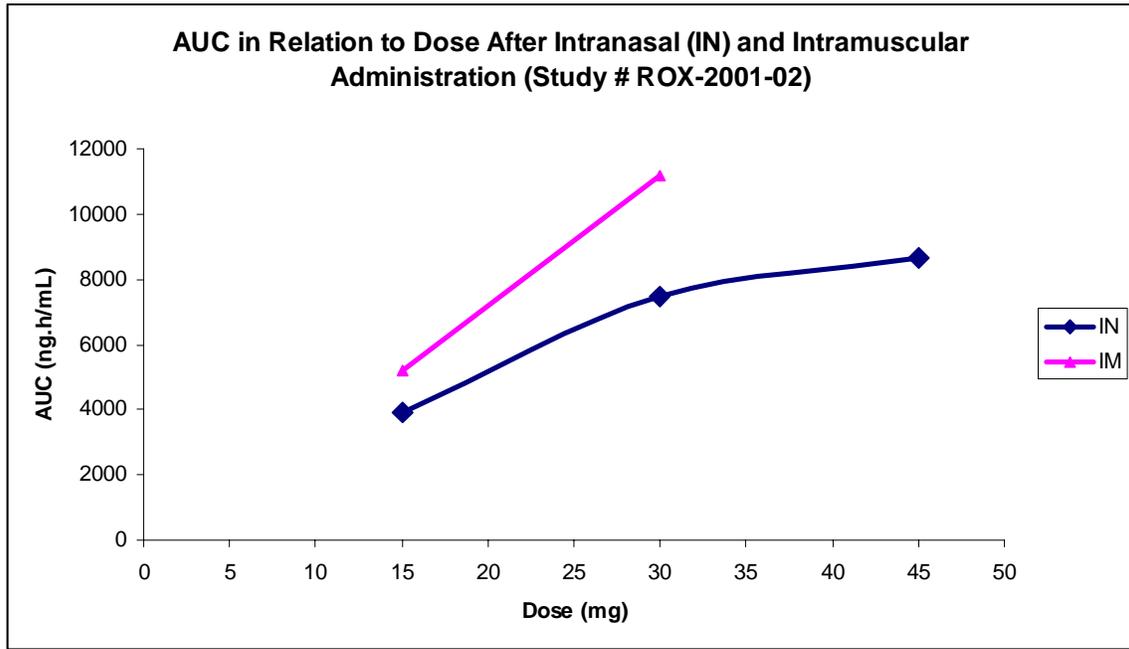
**Figure 2.2.3.1 Mean of Ketorolac Cmax After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**



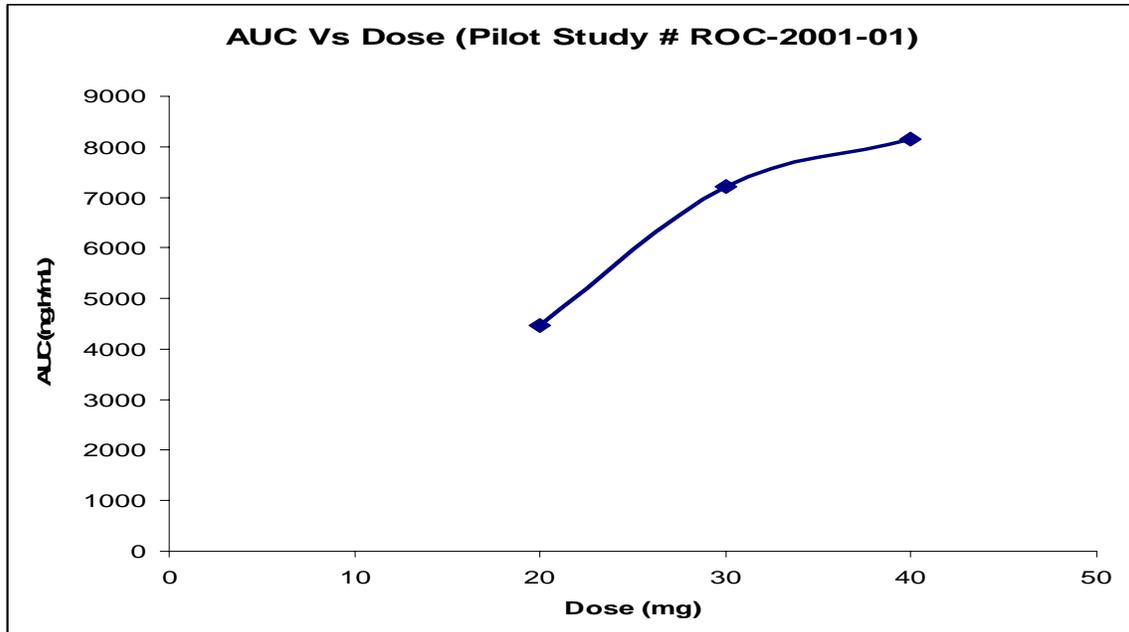
**Figure 2.2.3.2 Dose and Cmax Relationship After Intranasal Administration of Ketorolac Spray (Pilot Study # ROX-2001-01)**



**Figure 2.2.3.3 Mean Ketorolac AUC<sub>(0-inf)</sub> After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**



**Figure 2.2.3.4 Dose and AUC Relationship After Intranasal Administration of Ketorolac Spray (Pilot Study # ROX-2001-01)**



It should be noted that there was dose proportionality after IM administration up to 45 mg for both Cmax and AUC, but not after intranasal administration.

### **Justification for Dose Selection:**

Sponsor initiated the dose selection thought process based on population PK/PD modeling for ketorolac that was published back in 1996 (Mandema and Stanski, Clin. Pharmacol. Ther, 60 (6), 619-635, 1996). This paper was based on review of the safety and efficacy data from several clinical studies following IM administration. The covariates of the model accounted for the PK parameters, pain relief, and remedication. From this model, it was determined that about 25% of the population will achieve adequate pain relief with placebo. At doses of 10 mg, 30 mg, and 90 mg IM ketorolac, the success rate increased to 67%, 80%, and 85%, respectively. Since there were no added benefits between 30 mg and 90 mg, the authors concluded that 30 mg is the optimal dose for IM ketorolac. Based on this, sponsor tested 10 mg and 30 mg intranasal doses in phase II studies. The 10 mg dose did not show significant control of analgesia compared to placebo. Therefore, the 30 mg dose at a frequency of Q6-8 h was chosen for further development in Phase III program based on its onset and duration of action.

This information is also supported by several studies in this NDA in which the plasma levels achieved after intranasal administration was within the range of that achieved after IM doses of 15 mg and 30 mg (Studies # **ROX-2001-01 and ROX-2001-02, and ROX-2001-03**). The relative bioavailability of intranasal ketorolac to that of IM was approximately 73% at 15 mg dose and 60% at 30 mg dose (**Study # ROX 2001-02**).

### **2.2.3.2 Does this Drug Prolong the QT or QTc Interval?**

The sponsor did not conduct specific study to establish the effect of nasal spray on QTc prolongation. However, the label contains some general information and historical information related to the cardiovascular effect of the oral and the IM/IV products of ketorolac.

### **2.2.4 What are the PK characteristics of the drug?**

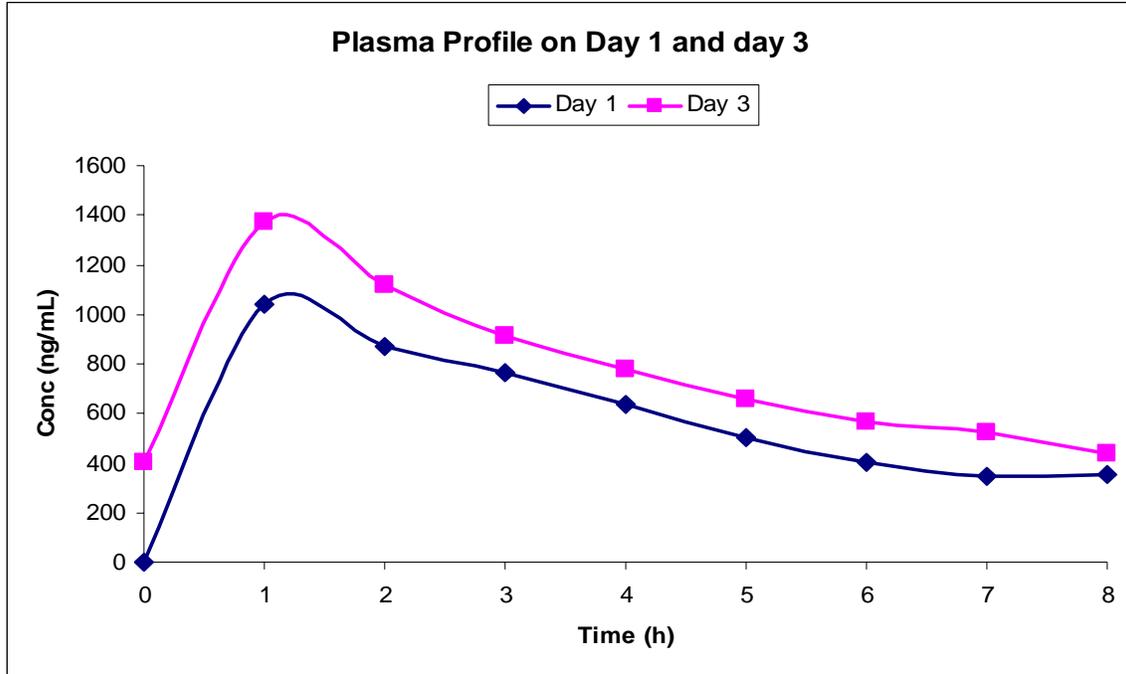
#### **2.2.4.1 What are the single and multiple dose PK parameters of ketorolac and its metabolites? How do the PK parameters change with time following chronic dosing?**

The drug is indicated for a short duration of 5 days. Based on ketorolac's half-life of about 5 hours, significant accumulation of the drug and its metabolites are not expected to occur. Nevertheless, the sponsor conducted two multiple dose studies at 30 mg dose level: one at Q6h regimen for 5 days (study # ROX-2001-04) and the other at Q8h regimen for 3 days (Study # ROX-2005-03).

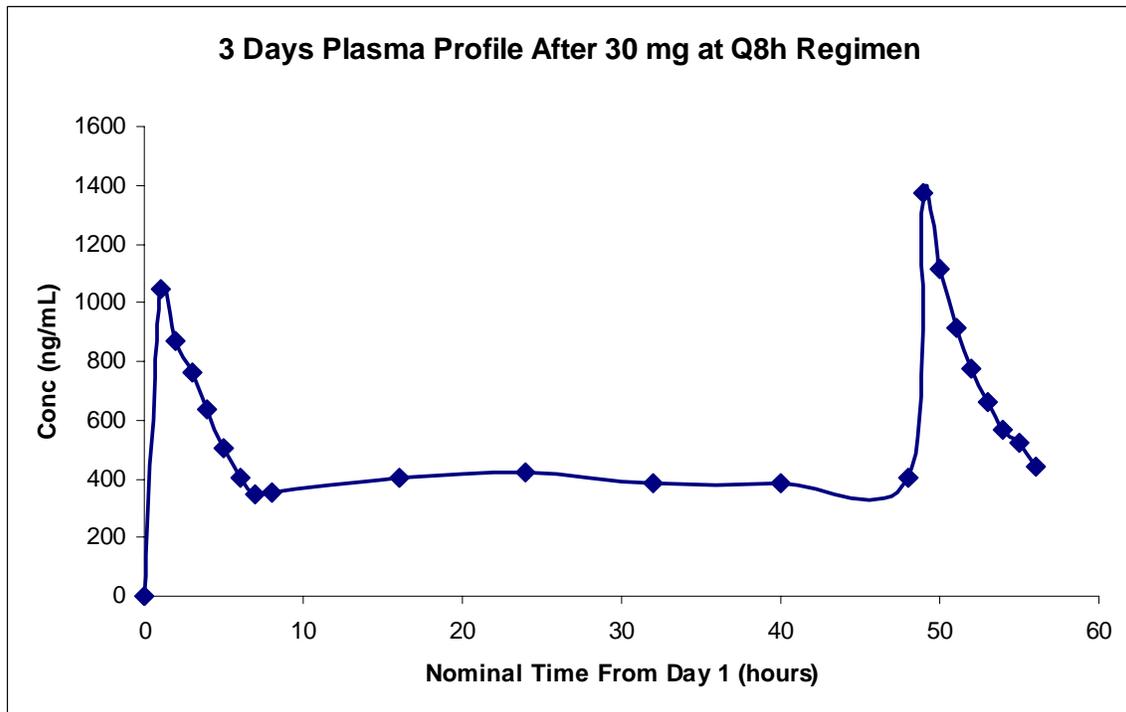
From both studies, the steady state level was achieved within 24 hours after either Q6h or Q8h dosing regimen. The exposure appears to be about 40% higher on Day 3 compared to Day 1 (**Figure 2.2.4.1 A and B**). Based on the limited duration of administration recommended for this drug (i.e. max 5 days) there is no concern of drug accumulation. It

should be noted that the C<sub>max</sub> occurs within 1 hour of administration in both multiple dose studies and single dose studies.

**Figure 2.2.4.1 A. Mean Plasma Concentration-Time Profile of Ketorolac on Day 1 and 3 (Study # ROX-2005-03)**



**Figure 2.2.4.1 B. Three Days Profile of ketorolac of 30 mg Dose (Study # ROX-2005-03)**



## 2.3 Intrinsic factors

### 2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Based on the currently approved label, ketorolac may be cleared more slowly in elderly and are more sensitive to the dose-related adverse effects of NSAIDs such as ulceration, bleeding, and perforation. Therefore, extreme caution should be exercised in elderly with reduction in dose. In addition, careful clinical monitoring must be used when treating the elderly with Toradol®.

Similarly, since ketorolac and its metabolites are eliminated primarily by the kidneys, caution should be exercised in patients with impaired renal function and should be closely monitored. Ketorolac is contraindicated in patients with severe renal dysfunction. Based on the approved label, it was reported that ketorolac caused acute renal failure, interstitial nephritis and nephrotic syndrome.

Across studies comparison and the literature, the PK in elderly appears to be comparable of nonelderly (**Table 2.3.1**). The PK in elderly and pediatric population is discussed in more detail in the next sections.

**Table 2.3.1. Summary of PK Parameters (Mean ± SD) Following IM and intranasal Singles Doses of Kerorolac in From Different Studies in Various Subpopulations.**

Population	Dose	N	Bioavailability (extent)	t <sub>max</sub> (min)	C <sub>max</sub> (µg/mL)	AUC <sub>0-∞</sub> (µg/mL.h)	t <sub>1/2</sub> (h)
IM Dose							
Adults <sup>a</sup>	10 mg	15	100%	45.6 ± 9.0	0.77 ± 0.12	5.19 ± 1.49	5.00 ± 1.88
Adults <sup>b</sup>	15 mg	54	100%	33 ± 21 <sup>c</sup>	1.14 ± 0.32 <sup>c</sup>		
Adults <sup>d</sup>	15 mg	15	100%	45 (15-90) <sup>e</sup>	1.16 ± 0.28	5.20 ± 2.08	5.00 ± 1.72
Adults <sup>b</sup>	30 mg	54	100%	44 ± 29	2.42 ± 0.68		
Adults <sup>d</sup>	30 mg	15	100%	45 (15-62) <sup>e</sup>	2.38 ± 0.43	11.15 ± 4.26	4.80 ± 1.18
Adults <sup>f</sup>	30 mg	12	100%	50.0 ± 14.8	2.24 ± 0.32	13.7 ± 4.0	5.21 ± 0.68
Adults <sup>g</sup>	30 mg	8	100%	45.0 ± 33	2.99 ± 1.03	11.3 ± 3.49	4.45 ± 0.39
Elderly <sup>g</sup>	30 mg	13	100%	58.2 ± 37.8	2.52 ± 0.77	15.3 ± 4.67	6.95 ± 1.39
Nominal IN Dose (actual dose)							
Pediatric <sup>h</sup>	15 mg (15.75 mg)	7		43 (23-364) <sup>e</sup>	1.15 ± 0.48	10.59 ± 7.82	6.68 ± 2.88
Adults <sup>d</sup>	15 (15.5) mg	15	73%	30 (15-60) <sup>e</sup>	0.91 ± 0.29	3.91 ± 1.57	4.76 ± 1.38
Pediatric <sup>h</sup>	30 (31.5) mg	13		47 (29-300) <sup>e</sup>	1.63 ± 0.54	11.95 ± 6.51	5.03 ± 2.06
Adults <sup>d</sup>	30 (31.5) mg	15	60%	45 (30-120) <sup>e</sup>	1.81 ± 0.88	7.48 ± 3.65	5.24 ± 1.33
Adults <sup>i</sup>	30 (31.5) mg	24		60 (15-120) <sup>e</sup>	1.63 ± 0.65	9.91 ± 4.35	5.58 ± 1.93
Adults <sup>j</sup>	30 (31.5) mg	15		45 (15-60) <sup>e</sup>	1.84 ± 1.00	6.89 ± 3.45	3.31 ± 0.96
Elderly <sup>j</sup>	30 (31.5) mg	13		45 (30-60) <sup>e</sup>	2.03 ± 1.07	8.79 ± 4.13	4.52 ± 1.14
Pooled <sup>k</sup>	30 (31.5) mg	188		42 <sup>l</sup>	1.24 (0.38, 3.27) <sup>l</sup>	8.10 ± 3.28 <sup>m</sup>	8.74 ± 1.69 <sup>m</sup>

a. Study in 15 normal volunteers (Mroszczak, 1990)

b. Derived from IM PK studies in 54 normal volunteers (ketorolac IM/IV label)

c. Mean value was simulated from observed plasma concentration data and SD was simulated from %CV of observed C<sub>max</sub> and t<sub>max</sub> data (ketorolac IM/IV label)

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- d. Study ROX-2001-02 in 15 non-elderly adult volunteers
- e. Median and range
- f. Study in 12 normal male volunteers (Mroszczak, 1990)
- g. Study in 8 young adults and 12 elderly volunteers (Jallad, 1990)
- h. Study ROX-2006-02 in 20 postoperative pediatric patients
- i. Study ROX-2007-03 in 24 adult volunteers with rhinitis
- j. Study ROX-2007-02 in 13 elderly and 15 non-elderly volunteers
- k. Population analysis in pooled data from 20 pediatric postoperative patients, 17 elderly and 151 non-elderly adult volunteers with and without rhinitis (ROXPOP-2008-01)
- l. Population  $C_{max}$  with 90%PI obtained from simulations (n=1000) at population  $t_{max}$  in non-elderly healthy subjects
- m. Mean  $\pm$  SD obtained from individual posterior parameter estimates in 102 non-elderly healthy adult subjects

### 2.3.1.1 Effect of Age:

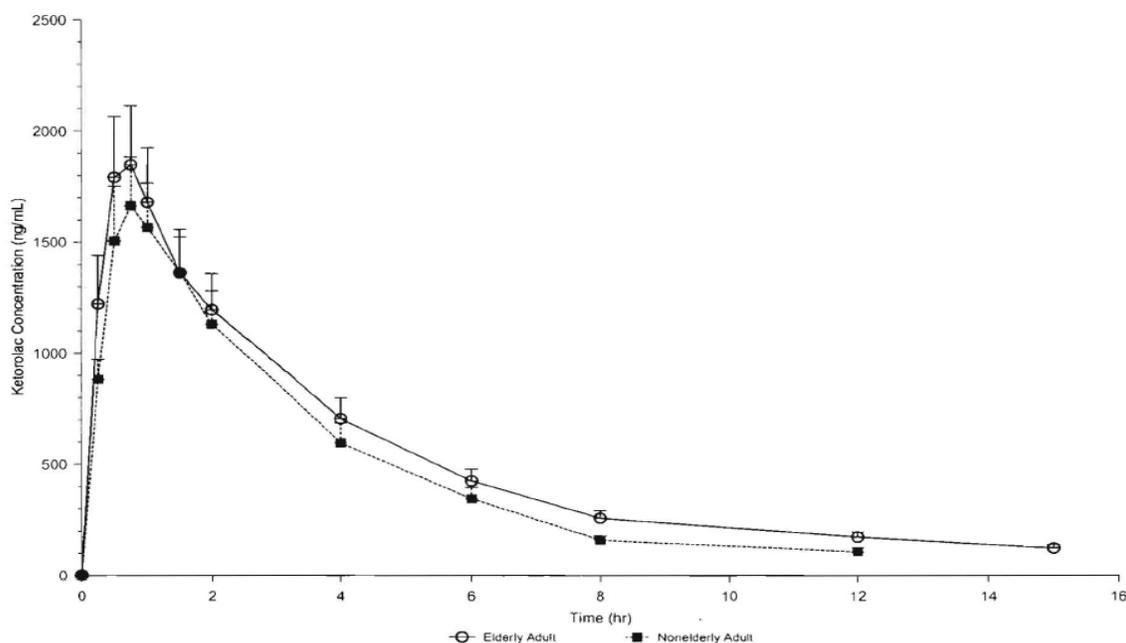
#### The PK in Elderly:

From the original NDA and the currently approved label, the half life of ketorolac appears to increase from 5 to 7 hours in the elderly 65 to 78 years of age compared with young healthy subjects between the ages of 24 to 35 years. There was little difference in  $C_{max}$  between elderly (2.52  $\mu\text{g/mL}$ ) and young adults (2.99  $\mu\text{g/mL}$ ).

Similarly, there was little difference in the PK of intranasal ketorolac between elderly subjects above the age of 65 years compared to those <65 years of age (Study # ROX 2007-02).

Overall, the plasma concentration-time profiles in elderly and nonelderly were comparable (Figure 2.3.1). The mean  $C_{max}$  in elderly was approximately 1780 ng/mL and 1840 ng/mL in nonelderly subjects. The  $AUC_{(0-last)}$  was slightly higher in elderly (~8000 ng.h/mL) compared to nonelderly (~6500 ng.h/mL).

**Figure 2.3.1 Mean Plasma Concentration-Time Profiles in Elderly and Nonelderly subjects (Study # ROX-2007-02)**



Overall, considering the variability of the data, the PK in elderly is comparable to that of non-elderly. The data from this study is comparable to that in the original NDA as described in the approved label.

Based on this, no change in the precaution and dosage and administration sections of the currently approved labeling in reference to elderly is warranted at this time.

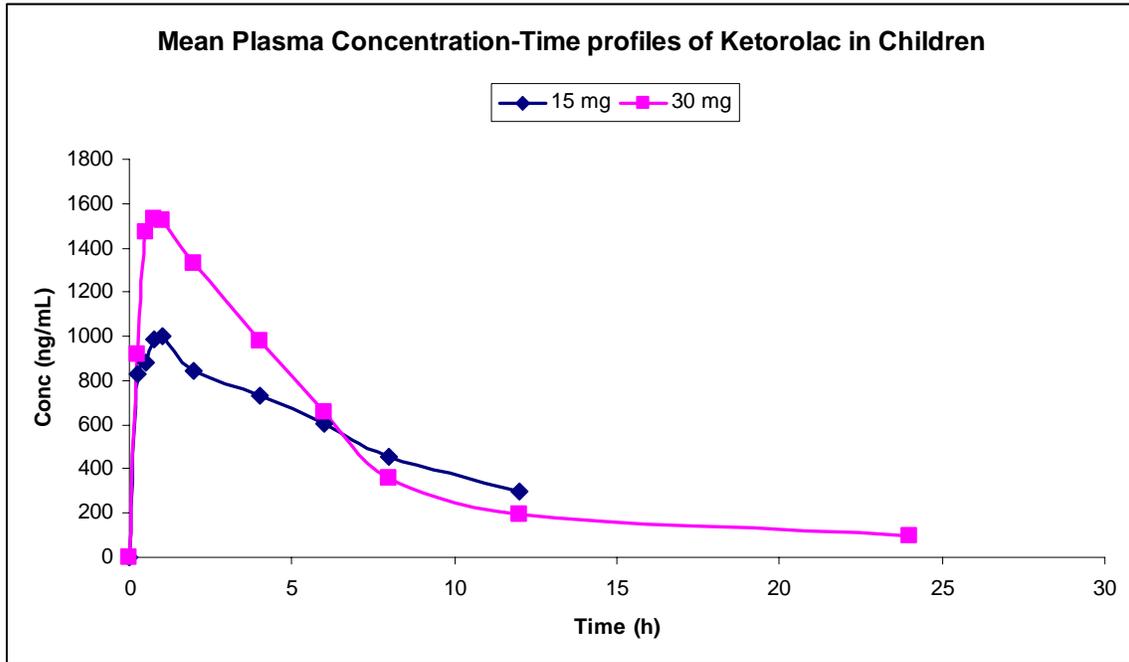
#### **The PK in Pediatrics:**

The drug is not indicated in pediatric population under the age of 17 years. The sponsor submitted a request for deferral of pediatric studies for intranasal ketorolac in this NDA. The IN product is delivered via a metered dose pump, calibrated to deliver a predefined dose appropriate for adult use only. (b) (4)

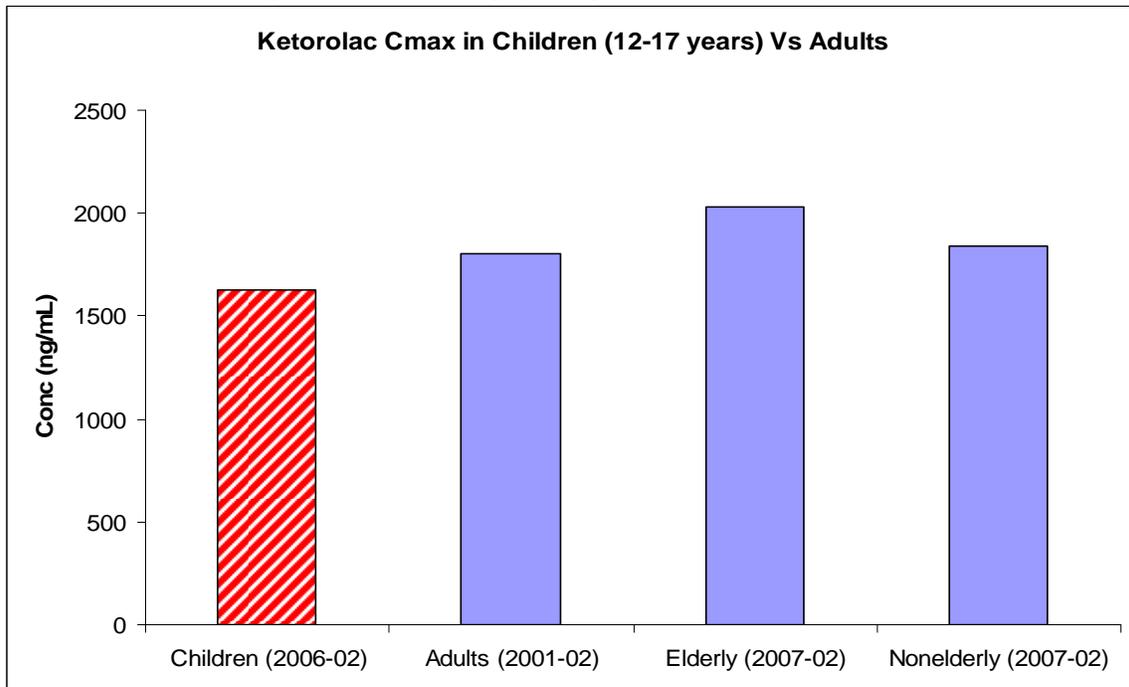


The PK of intranasal ketorolac was investigated in children between the ages of 12 to 17 years following single doses of 15 mg and 30 mg (**Study # ROX-2006-02**). One patient (subject 8) weighing 91 kg refused the second spray and therefore received 15 mg dose instead of the planned 30 mg dose. The plasma concentration-time profiles and exposure (C<sub>max</sub> and AUC) are shown in **Figure 2.3.2 and Table 2.3.2**, respectively. The AUC after 30 mg dose (in patients weighing  $\geq 50.0$  kg) was only about 12% higher (10% higher excluding subject 8) than that after 15 mg dose in patients weighing  $< 50.0$  kg. Overall, considering the variability across studies, the exposure (AUC) in the pediatric population appears to be about 25% higher to that previously obtained from adult subjects receiving a 31.5 mg intranasal dose. (**Figures 2.3.3 and 2.3.4 and Table 2.3.1**).

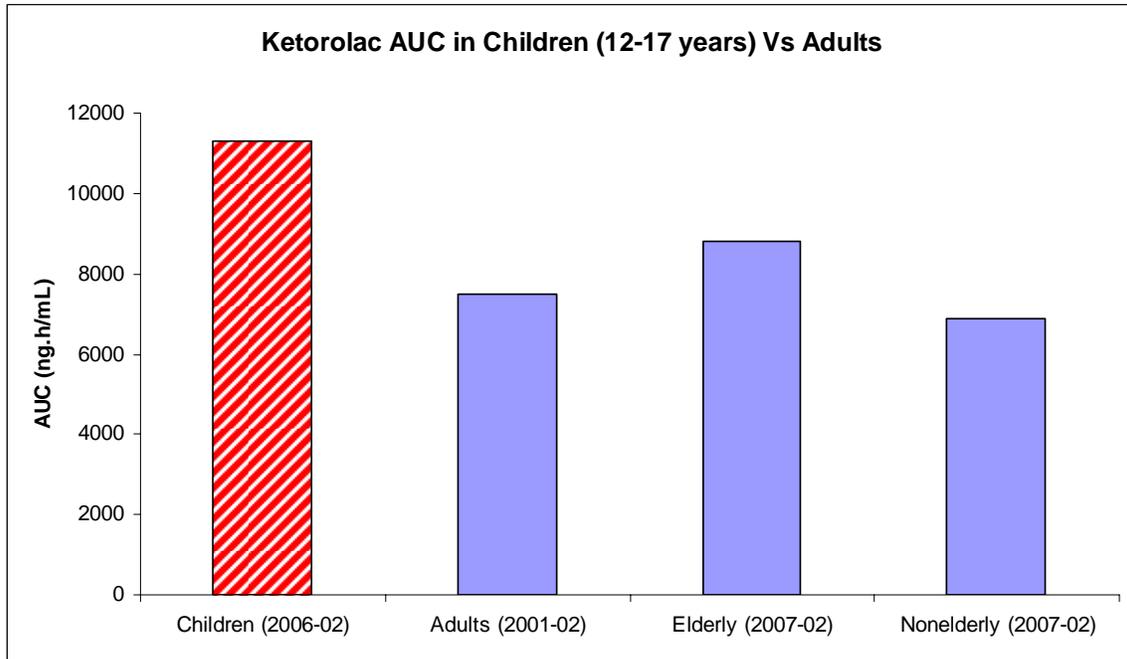
**Figure 2.3.2 Mean Plasma Concentration-Time Profiles of Ketorolac in Pediatric Patients After 15 mg and 30 mg Single Intranasal Doses (Study # ROX-2006-02)**



**Figure 2.3.3 Cross Studies Comparison of Mean Ketorolac C<sub>max</sub> Following 30 mg Single Intranasal Dose in Children (Study # ROX 2006-02), adults (Study # ROX 2001-02), and elderly and non-elderly (Study # ROX 2007-02)**



**Figure 2.3.4 Cross Studies Comparison of Mean Ketorolac AUC Following 30 mg Single Intranasal Dose in Children (Study # ROX 2006-02), adults (Study # ROX 2001-02), and elderly and non-elderly (Study # ROX 2007-02)**



**Table 2.3.2 Summary of Ketorolac PK Data in Pediatric Patients After 15 mg and 30 mg Single Intranasal Doses (Study # ROX-2006-02)**

Parameter	Summary Statistic	Dose Level	
		15 mg IN	30 mg IN
Number of subjects receiving treatment		7	13
$C_{max}$ (ng/mL)	n	7	13
	Mean	1153.896	1625.284
	SD	484.961	538.479
$T_{max}$ (h)	N	7	13
	Median	0.720	0.780
	Range	0.38 – 6.07	0.48 – 5.00
$AUC_{last}$ (ng.h/mL)	N	7	13
	Mean	9308.2	10662.1
	SD	6214.2	5383.5
$AUC$ (ng.h/mL)	N	6	12
	Mean	10590.7	11949.5
	SD	7818.4	6506.1
$AUC_{0-24}$ (ng.h/mL)	N	7	12
	Mean	9600.5	11317.2
	SD	5959.9	5666.1
$t_{1/2}$ (h)	N	6	12
	Mean	6.678	5.031
	SD	2.882	2.055
MRT (h)	N	6	12
	Mean	9.664	6.727
	SD	3.892	1.945

### **2.3.1.2 Effect of Gender, Race, and Weight:**

No formal study was conducted by the sponsor to characterize the effect of gender, race, or weight on the PK of intranasal ketorolac. From this NDA, based on limited data no differences were observed in the PK of intranasal ketorolac between females and males or due to race or weight. However, it should be noted that the approved IM package insert recommends half of the regular dose in patients with a body weight  $\leq 50.0$  kg compared to those weighing more than 50.0 kg. This same recommendation is being carried over to the intranasal product as well. The IM package insert also states that no PK differences due to race have been identified.

### **2.3.1.3 Effect of Renal Impairment**

It is well documented that the long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Since ketorolac is eliminated primarily by the kidneys and it is known to cause renal toxicity, its clearance is expected to be reduced in patients with renal insufficiency. Therefore, the drug is contraindicated in patients with severe renal impairment.

No formal study was conducted with intranasal ketorolac in patients with renal impairment. However, based on the current approved label, the AUC of ketorolac increased by approximately 100% in patients with renal impairment compared to healthy subjects.

### **2.3.1.4 Effect of Liver Function (Hepatic Impairment)**

No formal study was conducted with intranasal ketorolac in patients with liver impairment. However, based on the current approved label, no significant difference was observed in ketorolac PK between patients with liver disease and healthy subjects.

## 2.4 Extrinsic factors

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

According to the currently approved label, ketorolac does not appear to be either an enzyme inhibitor or inducer. Therefore, its potential interaction with other concomitantly administered drugs is minimal. However, the currently approved label lists several drugs that may interact with oral and injectable ketorolac. These include warfarin, NSAIDs, aspirin, probenecid, diuretics, and lithium. Most of these interactions are non-metabolically based but rather mechanistic or pharmacodynamic interaction based.

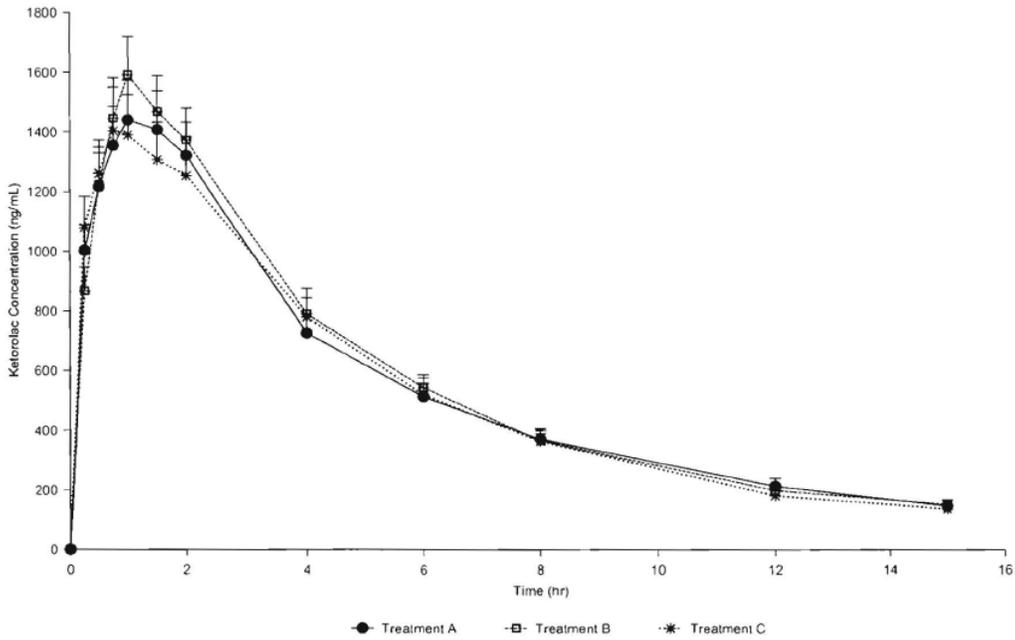
Three additional local drug-drug interaction studies were conducted with intranasal ketorolac spray. The objectives of these studies were to investigate the effect of other intranasal sprays that may concomitantly be used on the local absorption and PK of intranasal ketorolac.

The sponsor selected two commonly used intranasal preparations, oxymetazoline (OTC Afrin® in US) and fluticasone propionate (Rx Flonase® in US). These three studies were conducted in healthy subjects (**ROX-2006-03, and ROX 2006-04**) and in patients with allergic rhinitis (**Study # ROX-2007-03**).

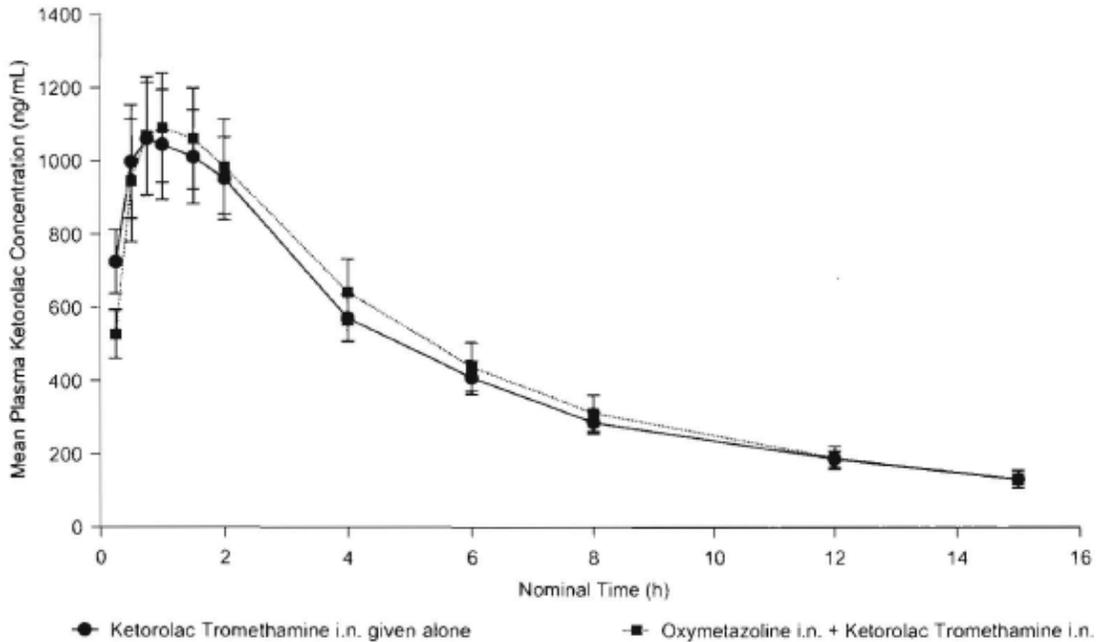
Two of these studies were conducted after a single ketorolac dose of 30 mg (15 mg in each nostril) administered 30 minutes after oxymetazoline (3 sprays) or fluticasone propionate (200 µg) administration (**Studies # ROX-2006-03 and ROX-2007-03**). One study was conducted after multiple doses of fluticasone propionate. In this study, the same ketorolac dose was give (i.e., 30 mg) alone on Day 1 and 30 minutes after the last dose of fluticasone of 200 µg on Day 6 (**Study # ROX-2006-04**). Fluticasone nasal spray was administered once daily at 200 µg (2 x 50 µg) in each nostril for 5 days.

From the three studies, it can be concluded that there was no major effect of either fluticasone or oxymetazoline on the absorption of intranasal ketorolac following single doses and multiple doses in healthy subjects and patients with allergic rhinitis (**Figures 2.4.1-2.4.3**)

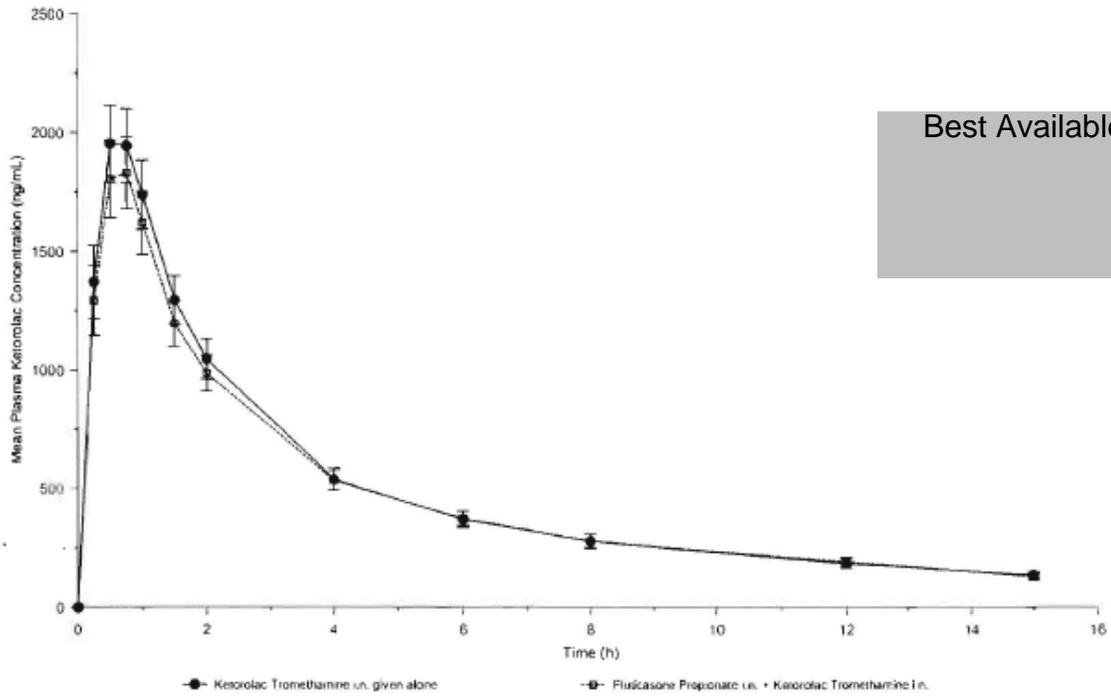
**Figure 2.4.1 Mean ( $\pm$  SE) Plasma Concentration-Time Profiles When Administered Alone or with Oxymetazoline or Fluticasone in 24 Patients with Allergic Rhinitis (Study # ROX-2007-03)**



**Figure 2.4.2. Mean ( $\pm$  SE) Plasma Concentration-Time Profiles Ketorolac when Given Alone or With Oxymetazoline in 21 Healthy Subjects (Study # ROX-2006-03)**



**Figure 2.4.3. Mean ( $\pm$  SE) Plasma Concentration-Time Profiles Ketorolac when Given Alone on Day 1 or With Fluticasone on Day 6 After Multiple Dose in 36 Healthy Subjects (Study # ROX-2006-04)**



Based on the data from these studies, it can be concluded that no dose adjustment is necessary when ketorolac is administered with either fluticasone propionate or oxymetazoline.

## 2.5 General Biopharmaceutics

### 2.5.1 What is the BCS Class Classification for Ketorolac?

Ketorolac exhibits aqueous solubility a (b) (4). Although, the drug appears to be sufficiently absorbed, the sponsor did not provide information about the permeability of the drug to be used in BCS classification. However, since this is intranasal route of administration, lack of this information is not critical.

#### 2.5.2.1 What is the Absolute Bioavailability of Ketorolac?

Based on a single dose intranasal ketorolac study the absolute bioavailability in reference to intravenous ketorolac was approximately 60% to 85%, depending on the strength of the solution being administered (**Study # REC 1993-01**).

The study was conducted as a single dose crossover in 12 healthy male subjects with a washout period of one week between treatments as follows:

#### Group I (n=6 subjects):

**Formulation B1:** Single 10 mg intranasal dose of 5% solution (1 spray in each nostril)

**Formulation B2:** Single 30 mg intranasal dose of 15% solution with (b) (4) (1 spray in each nostril).

**IV Formulation:** Single 10 mg **intravenous (IV)** dose (10 mg/mL IV solution).

#### Group II (n=6 subjects):

**Formulation A:** Single 10 mg intranasal dose of 5% solution (1 spray in each nostril).

**Formulation B1:** Single 10 mg intranasal dose of 5% solution with (b) (4) (1 spray in each nostril).

**Formulation C:** Single 10 mg intranasal dose of 5% solution with (b) (4) (1 spray in each nostril).

The absolute bioavailability of ketorolac after intranasal route relative to 10 mg intravenous administration was 86% at 10 mg dose of 5% solution and 56% at 30 mg dose of 15% solution with (b) (4) (**Table 2.5.1, Group I and Figures 2.5.1 and 2.5.2**). The plasma concentration-time profiles show the C<sub>max</sub> occurs within about 1 hour of intranasal administration (**Figure 2.5.4**). The most relevant data is for the 30 mg dose of 15% solution (F = ~60%) which represents the proposed to be marketed strength/formulation.

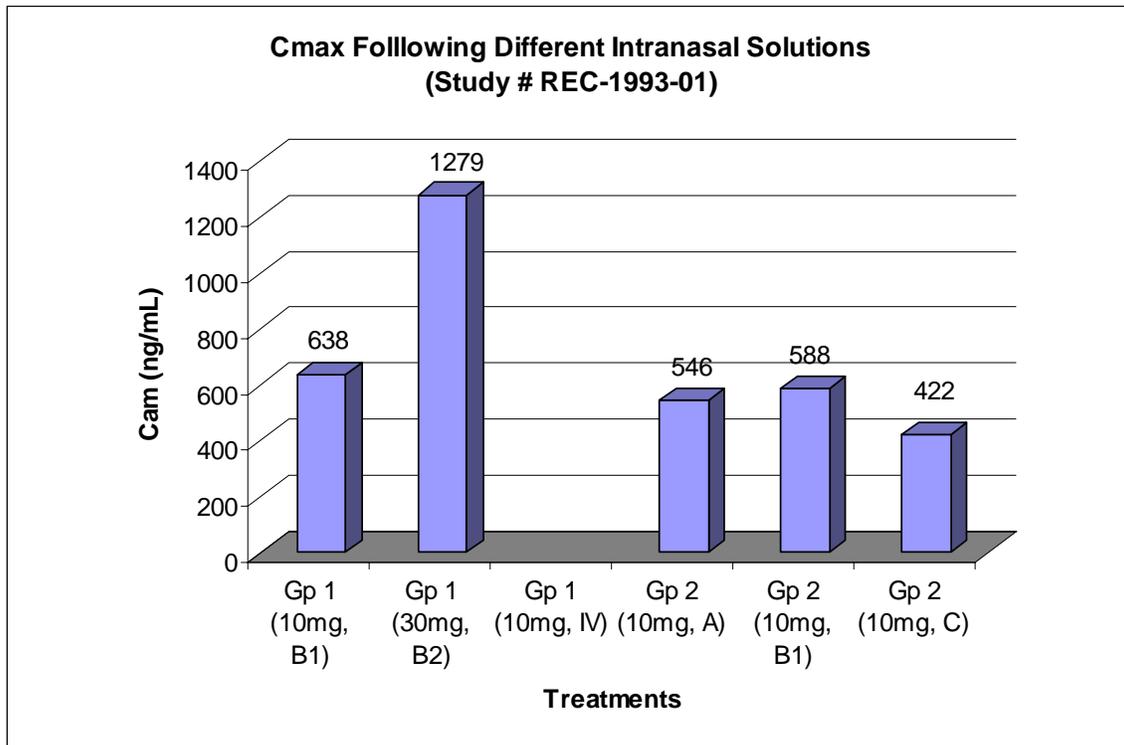
**Table 2.5.1. Absolute Bioavailability of Intranasal Ketorolac Spray (Study # REC-1993-01)**

	Formulation	Treatment	Dose (mg)	Spray Solution Concentration	Mean AUC (*) (ng·h/mL)	Mean Cmax (*) (ng/mL)	AUC ratio	Cmax ratio	F%
Group 1 Subjects N° 1 - 6	I.V. solution	C	10	-	3144,5	-	-	-	-
	B1	A	10	5%	2693,4	-	0,86	-	86
	B2	B	30	15%	5252,5	-	0,56 (§)	-	56
Group 2 Subjects N° 7 - 12	A	A	10	5%	2786,0	502,1	-	-	-
	B1	B	10	5%	2701,6	541,2	0,98	1,08	98
	C	C	10	5%	2519,3	364,8	0,91	0,73	91

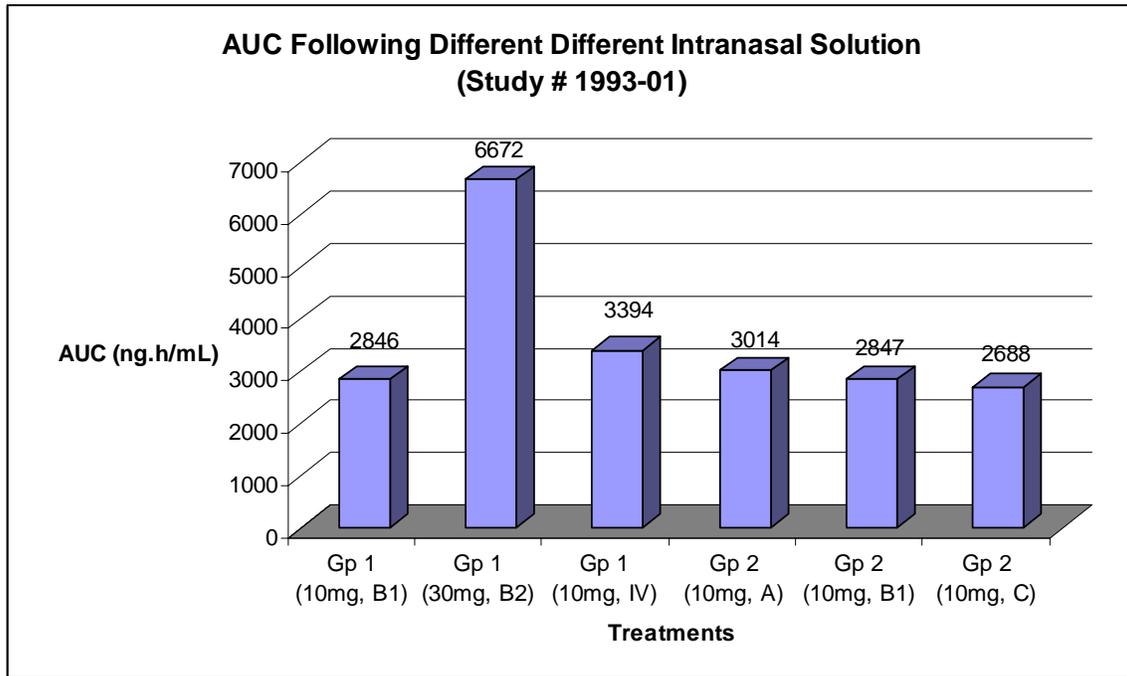
(\*) Geometric Mean  
(§) Dose corrected

	Formulation	Treatment : Dose administered - ( formulation with Lot N° )
Subjects N° 1 - 6	I.V. solution	C : ketorolac tromethamine 10 mg - ( ampoules Lot N° 371/17 )
	B1	A : ketorolac tromethamine 10 mg - ( 5% spray solution B1 - Lot N° 429/80 ) (b) (4)
	B2	B : ketorolac tromethamine 30 mg - ( 15% spray solution B2 - Lot N° 429/84 ) (b) (4)
Subjects N° 7 - 12	A	A : ketorolac tromethamine 10 mg - ( 5% spray solution A - Lot N° 429/78 ) (b) (4)
	B1	B : ketorolac tromethamine 10 mg - ( 5% spray solution B1 - Lot N° 429/80 ) (b) (4)
	C	C : ketorolac tromethamine 10 mg - ( 5% spray solution C - Lot N° 429/82 ) (b) (4)

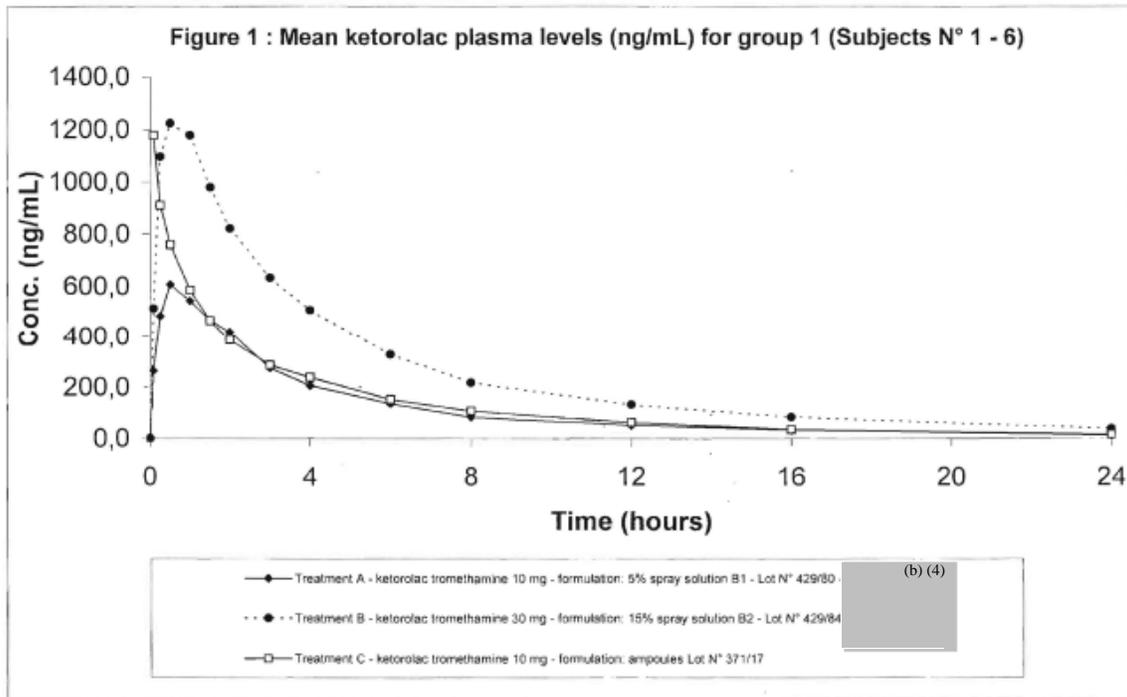
**Figure 2.5.1 Ketorolac Cmax Following Intranasal Solutions (Study # REC-1993-01)**



**Figure 2.5.2 Ketorolac AUC (0-inf) Following Intranasal and Intravenous Solutions (Study # REC-1993-01)**



**Figure 2.5.3 Plasma Concentration-Time Profiles of Intravenous (IV) and Intranasal (IN) Ketorolac (Study # REC-1003-01)**



From this study, it can be concluded that the ketorolac is sufficiently absorbed after intranasal administration. Considering the high variability in the data and the limited sample size of the study, the absolute bioavailability appears to be in the range of approximately 60% to 85%. However, there is trend for less than dose proportional increase in exposure as demonstrated for both Cmax and AUC.

### 2.5.2 What is the Effect of Food on the BA of Ketorolac?

Not applicable.

### 2.5.3 Was the to-be-Marketed Formulation Used in the Clinical Trials?

According to the sponsor, the formulation the clinical trials are the final-to-be marketed (Table 2.5.2, see also CMC review).

**Table 2.5.2. Composition of Nasal Spray Drug Product Solution**

Table 2.3.P.1-1. Drug Product Unit Composition						
Ingredient	Amount					Function
	mg/spray <sup>a</sup>	(b) (4)	(b) (4)	(b) (4)	mg/bottle <sup>c</sup>	
		(b) (4)	(b) (4)	(b) (4)	8 sprays (b) (4)	
Drug Substance:						
Ketorolac Tromethamine USP	15.75	(b) (4)	(b) (4)	(b) (4)	126.0 (b) (4)	Active ingredient
Excipients:						(b) (4)
Edetate Disodium USP						
Monobasic Potassium Phosphate (b) (4)						
Sodium Hydroxide (b) (4)	pH 7.2	f ( (	f ( (	f ( (	pH 7.2	pH adjustment
(b) (4) Water for Injection USP	q.s. ad	q	c	q	q (b) (4)	(b) (4)
Total					(b) (4)	

<sup>a</sup> Based on a nominal spray of 100 µL (=105 mg) per actuation.  
<sup>b</sup> The density of the formulation at ambient temperatures is equal to 1.05 g/mL.  
<sup>c</sup> The stated values are based on 8 sprays = 840 mg with an overfill to give a nominal fill weight of 1.7 g/bottle.

As show in the above table, this is a simple formulation/solution containing 15% ketorolac (b) (4) without (b) (4). However, it should be noted that in the early developmental studies, the sponsor tested several percentage of ketorolac ranging from 1.5% to 22.5% (b) (4). However, all subsequent clinical pharmacology studies and Phase III studies used the final-to-be marketed formulation containing 15% ketorolac (b) (4).

In terms of delivery device, in Phase I and II the intranasal ketorolac was delivered using single-dose and bi-dose metered pumps (b) (4). In Phase II, a multi-dose metered pump was used (b) (4). The multi-dose pump will be supplied for commercial production. The same pump assembly and materials of construction used for Phase III will be used in commercial production. Also, based on *in vitro* data, it is doesn't appear there is difference in delivery between a single dose pump, bi-dose and multi-dose pumps (see chemistry review by Dr. Joseph Leginus dated June 22, 2009).

#### **2.5.4 What are the Biopharmaceutical Characteristics of the Products?**

As indicated earlier, the final product contains 15% w/w filled in a multidose Type I clear glass bottle attached with metered/dose pump to deliver 100  $\mu$ L (15.75 mg) volume. The nominal fill weight is ~1.7 gram/bottle, which is equivalent to approximately (b) (4) of the solution. The unit is intended to deliver a maximum of 8 actuations per day. Then it must be discarded after 24 hours. Each actuation (100  $\mu$ L) will deliver 15.75 mg dose of ketorolac per nostril. In this case each dose is 31.5 mg (2 x 15.75 mg).

## 2.6 Analytical Section

Ketorolac concentrations in plasma were determined by two main validated HPLC methods with MS/MS detection (Method # 100/001 and 193/001). The lower limit of quantification (LLQ) of method # 100/0001 was 10 ng/mL. The calibration curve was linear over 10-3000 ng/mL and the inter-assay precision (% CV) ranged from 0.83-18.29% (Table 2.6.1).

The LLQ of the second method (# 193/001) was 50 ng/mL. The linearity of the calibration curve is 50 to 5000 ng/ml. The % CV is ranging from ~3% to 11% at LLQ levels and within the range of the calibration curve (Table 2.6.1).

**Table 2.6.1 Summary of Bioanalytical Methods Validation Data Used in this NDA**

Method	Study	LLQ			Linearity		Inter-assay	
		value (ng/mL)	Bias (%)	CV (%)	Range (ng/mL)	Bias (%)	CV (%)	
(b) (4)	REC-1993-01	10	a	a	a	a	a	
	ROX-2001-01	10.05	-0.06	8.76	10.05 to 2999.88	-2.75 to 2.14	11.05 to 18.29	
	ROX-2001-02	10.05	0.30	8.38	10.05 to 2999.88	1.00 to 4.66	9.48 to 12.26	
	ROX-2001-04	76.84	-3.98	a	76.84 to 2992.56	-8.90 to 1.33	0.83 to 4.92	
(b) (4)	ROX-2005-03 <sup>b</sup>	50.34	-3.75	8.14	50.34 to 4983.30	-4.10 to 2.98	4.90 to 6.42	
	ROX-2006-02 <sup>b</sup>	50.12	0.40	8.60	50.12 to 4981.50	-3.49 to 5.45	5.67 to 9.15	
	ROX-2006-03 <sup>b</sup>	49.40	0.40	7.44	49.40 to 4989.40	1.33 to 5.83	3.68 to 5.77	
	ROX-2006-04 <sup>b</sup> (system 10)	49.40	2.00	5.82	49.40 to 4989.40	-2.43 to 3.31	6.10 to 10.20	
	(system 6)	49.40	2.25	4.05	49.40 to 4989.40	-1.24 to 11.68	3.62 to 7.04	
	ROX-2007-02 <sup>b</sup>	50.07	-0.01	6.11	50.07 to 5006.50	-0.38 to 1.94	2.99 to 9.94	
	ROX-2007-03 <sup>b</sup>	50.12	0.44	8.11	50.12 to 4981.50	-5.46 to 0.65	5.81 to 11.66	

a. Not reported

b. Summarized in 2.7.2

The LLQ value of 50 ng/mL reported in the second method may not affect the overall outcome of PK data. The C<sub>max</sub> (~1500 ng/mL) after 30 mg dose is approximately 30 fold higher than the LLQ of the assay. Therefore, the margin of error at about the LLQ of 50 ng/ml would be insignificant to affect the overall plasma profile.

## 4.2 Selected Individual Study Review:

### 4.2.1 Study # REC 1993-01 (Pilot Absolute Bioavailability Study):

**Objectives:** The objective is to determine the absolute bioavailability of different ketorolac solutions after intranasal administration (IN) in healthy subjects.

#### Study Design:

This is a single dose crossover study in 12 healthy male subjects with a washout period of one week between treatments as follows:

#### Group I (n=6 subjects):

**Formulation B1:** Single 10 mg intranasal dose of 5% solution (1 spray in each nostril)

**Formulation B2:** Single 30 mg intranasal dose of 15% solution with (b) (4) (1 spray in each nostril).

**IV Formulation:** Single 10 mg **intravenous (IV)** dose (10 mg/mL IV solution).

#### Group II (n=6 subjects):

**Formulation A:** Single 10 mg intranasal dose of 5% solution (1 spray in each nostril).

**Formulation B1:** Single 10 mg intranasal dose of 5% solution with (b) (4) (1 spray in each nostril).

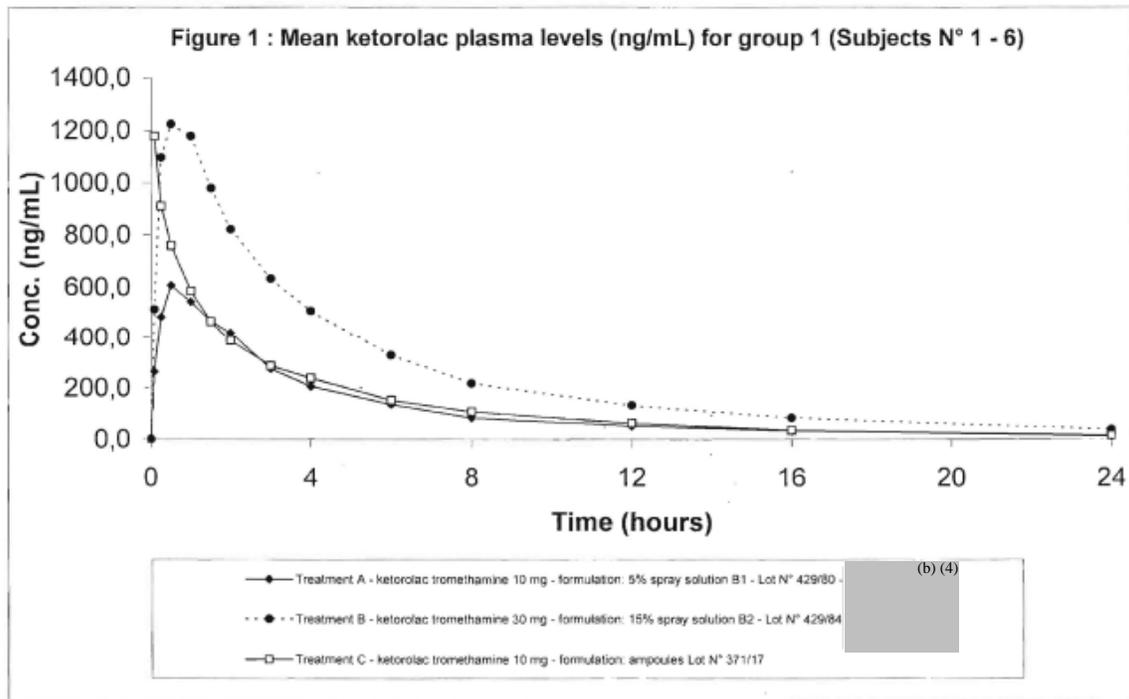
**Formulation C:** Single 10 mg intranasal dose of 5% solution with (b) (4) (1 spray in each nostril).

Blood was collected over 24 hours.

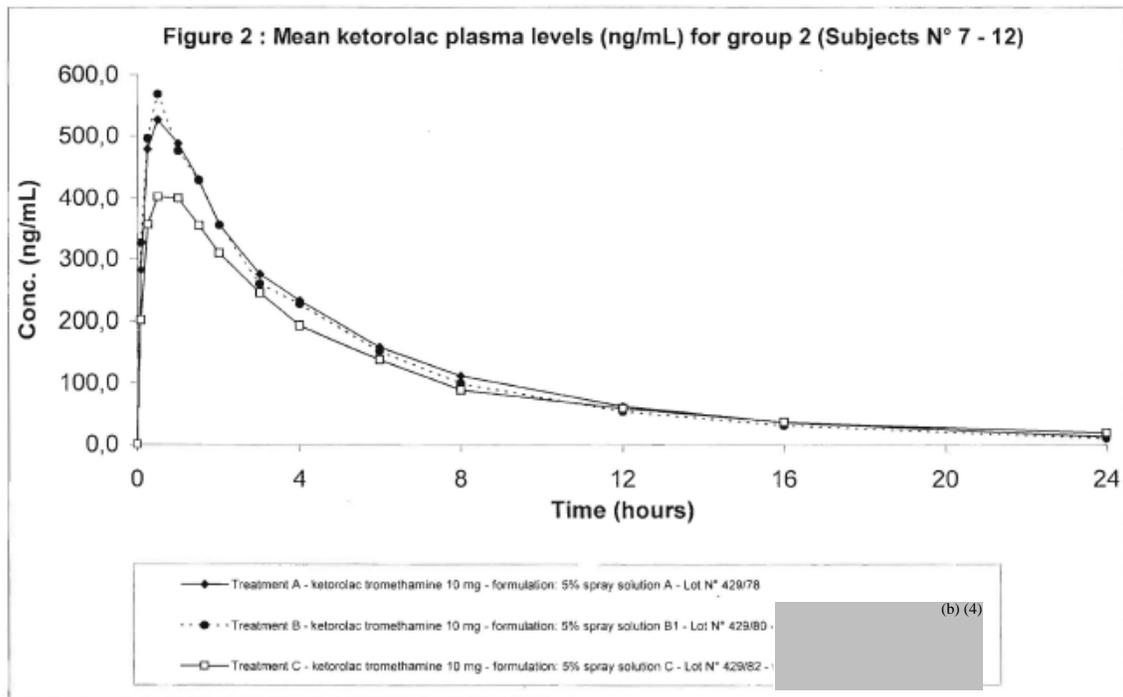
#### Results:

- There was less than proportional increase in both C<sub>max</sub> and AUC with increase in ketorolac intranasal dose from 10 mg to 30 mg (**Figures 4.2.1.1 to 4.2.1.4 and Tables 4.2.1.1 to 4.2.1.7**).
- (b) (4)
- The absolute bioavailability of IN route relative to 10 mg intravenous administration was 86% at 10 mg dose of 5% solution and 56% at 30 mg dose of 15% solution with (b) (4) (**Table 4.2.1.7, Group I**). However, the bioavailability of 5% solution at 10 mg dose was 98% (b) (4) and 91% (b) (4) relative to 10 mg dose of 5 % solution (b) (4) (**Table 4.2.1.7, Group II**).

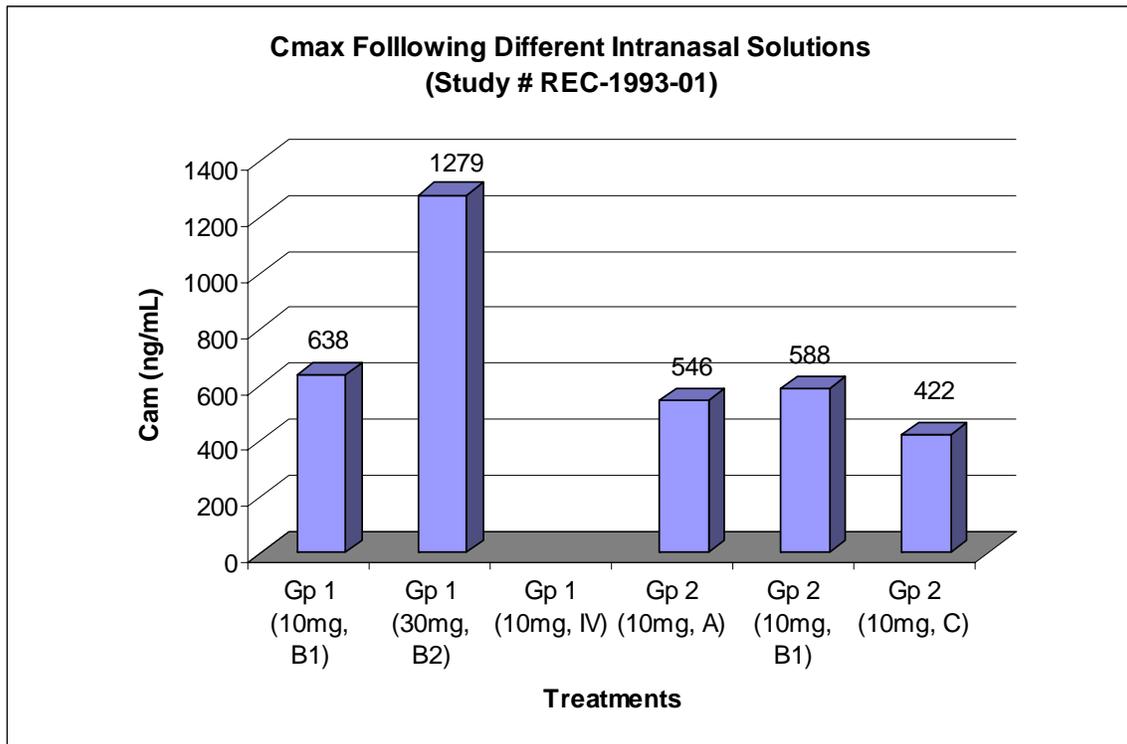
**Figure 4.2.1.1. Plasma Concentration-Time Profiles of Intravenous (IV) and Intranasal (IN) Ketorolac (Study # REC-1993-01)**



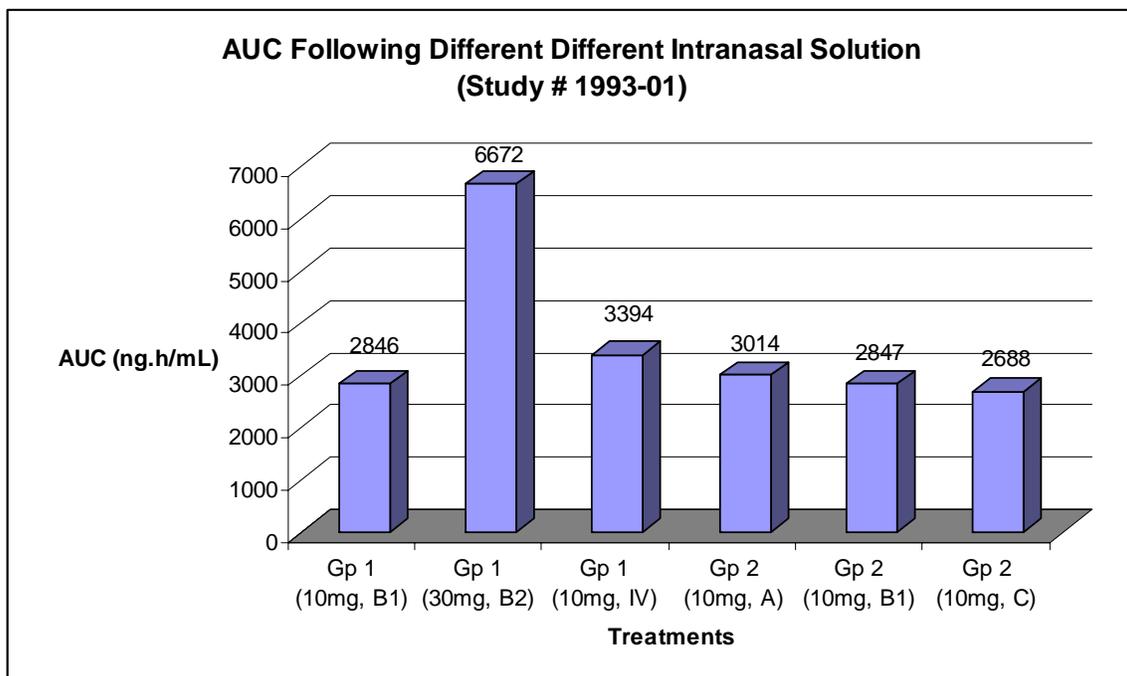
**Figure 4.2.1.2. Plasma Concentration-Time Profiles Absolute Bioavailability of Intranasal Ketorolac Spray (Study # REC-1993-01)**



**Figure 4.2.1.3. Ketorolac Cmax Following Intranasal Solutions (Study # REC-1993-01)**



**Figure 4.2.1.4. Ketorolac AUC (0-inf) Following Intranasal and Intravenous Solutions (Study # REC-1993-01)**



**Table 4.2.1.1. PK Parameters (Group 1, Formulation B1) (Study # 1993-01)**

Group 1		Treatment A : ketorolac tromethamine 10 mg Formulation : 5% spray solution B1 - Lot N° 429/80 - (b) (4)			
Subject N°	AUCt (ng×h/mL)	AUC (ng×h/mL)	Cmax (ng/mL)	tmax (h)	t1/2 (h)
1	3084	3226	908	0,5	6,2
2	1510	1603	482	0,5	4,3
3	2989	3227	572	1,0	6,8
4	2808	2887	843	0,5	3,3
5	1788	1852	415	0,5	3,3
6	3981	4279	609	2,0	6,8
n	6	6	6	6	6
min	1510	1603	415	0,5	3,3
max	3981	4279	908	2	6,8
Median	2698,5	3056,5	590,5	0,5	5,3
Mean	2693,3	2845,7	638,2	0,8	5,1
St. Dev.	909,0	987,7	197,1	0,6	1,7
Geom. Mean	2555,0	2693,4	613,5	0,7	4,9

**Table 4.2.1.2. PK Parameters (Group 1, Formulation B) (Study # 1993-01)**

Group 1		Treatment B : ketorolac tromethamine 30 mg Formulation : 15% spray solution B2 - Lot N° 429/84 - (b) (4)			
Subject N°	AUCt (ng×h/mL)	AUC (ng×h/mL)	Cmax (ng/mL)	tmax (h)	t1/2 (h)
1	1140	1199	356	0,083	3,3
2	5659	5814	1554	0,5	4,9
3	13088	14046	1732	1,0	6,5
4	3605	3683	913	0,25	3,0
5	6990	7174	1928	0,25	4,0
6	7356	8117	1190	0,5	7,7
n	6	6	6	6	6
min	1140	1199	356	0,083	3
max	13088	14046	1928	1	7,7
Median	6324,5	6494	1372	0,4	4,5
Mean	6306,3	6672,2	1278,8	0,4	4,9
St. Dev.	4046,9	4389,5	582,4	0,3	1,9
Geom. Mean	5001,4	5252,5	1123,1	0,3	4,6

**Table 4.2.1.3. PK Parameters Following IV administration (Group 1, Formulation 10 mg/mL IV solution) (Study # 1993-01)**

Group 1		Treatment C : ketorolac tromethamine 10 mg Formulation : ampoules Lot N° 371/17				
Subject N°	AUCt (ng×h/mL)	AUC (ng×h/mL)	β (1/h)	t1/2 (h)	CL (mL/min)	Vdβ (L)
1	4204	4361	0,1438	4,8	25,9	10,8
2	2070	2146	0,1926	3,6	52,7	16,4
3	3788	3992	0,1129	6,1	28,3	15,0
4	1648	1758	0,3522	2,0	64,3	11,0
5	2885	2747	0,2271	3,1	41,1	10,9
6	6025	5358	0,1237	5,6	21,1	10,2
n	6	6	6	6	6	6
min	1648	1758	0,1129	2	21,1	10,2
max	6025	5358	0,3522	6,1	64,3	16,4
Median	3236,5	3369,5	0,1682	4,2	34,7	10,95
Mean	3236,7	3393,7	0,1921	4,2	38,9	12,4
St. Dev.	1313,6	1400,2	0,0896	1,6	17,0	2,6
Geom. Mean	3002,7	3144,5	0,1772	3,9	35,9	12,2

**Table 4.2.1.4. PK Parameters (Group 2, Formulation A) (Study # 1993-01)**

Group 2		Treatment A : ketorolac tromethamine 10 mg Formulation : 5% spray solution A - Lot N° 429/78			
Subject N°	AUCt (ng×h/mL)	AUC (ng×h/mL)	Cmax (ng/mL)	tmax (h)	t1/2 (h)
7	2905	3048	622	0,25	3,5
8	3378	3800	517	0,5	7,0
9	2541	2757	458	0,25	7,3
10	958	1083	201	0,5	4,8
11	4386	4647	819	1,0	6,8
12	2877	2956	664	0,5	4,8
n	6	6	6	6	6
min	958	1083	201	0,25	3,5
max	4386	4647	819	1,0	7,3
Median	2891	3001	569,5	0,5	5,8
Mean	2840,8	3014,8	546,5	0,5	5,7
St. Dev.	1124,0	1167,0	210,8	0,3	1,9
Geom. Mean	2589,4	2768,0	502,1	0,4	5,5

**Table 4.2.1.5. PK Parameters (Group 2, Formulation B1 (b) (4)) (Study # 1993-01)**

Group 2		Treatment B : ketorolac tromethamine 10 mg Formulation : 5% spray solution B1 - Lot N° 429/80 - (b) (4)			
Subject N°	AUCt (ng×h/mL)	AUC (ng×h/mL)	Cmax (ng/mL)	tmax (h)	t1/2 (h)
7	3073	3169	613	0,5	4,8
8	1942	2030	362	0,25	4,9
9	4324	4473	1109	0,5	4,5
10	1494	1613	339	0,5	4,2
11	2740	3100	626	1,0	6,4
12	2595	2702	481	0,5	5,0
n	6	6	6	6	6
min	1494	1613	339	0,25	4,2
max	4324	4473	1109	1,0	6,4
Median	2667,5	2901	547	0,5	4,9
Mean	2694,7	2847,8	588,3	0,5	5,0
St. Dev.	951,6	1002,3	282,1	0,2	0,8
Geom. Mean	2548,7	2701,6	541,2	0,5	4,9

**Table 4.2.1.6. PK Parameters (Group 2, Formulation C (b) (4)) (Study # 1993-01)**

Group 2		Treatment C : ketorolac tromethamine 10 mg Formulation : 5% spray solution C - Lot N° 429/82 - (b) (4)			
Subject N°	AUCt (ng×h/mL)	AUC (ng×h/mL)	Cmax (ng/mL)	tmax (h)	t1/2 (h)
7	3355	3499	528	1,5	5,3
8	1601	1792	180	1,0	7,2
9	3067	3255	531	0,5	6,2
10	1405	1669	192	0,5	10,5
11	3771	4073	797	0,5	6,9
12	1688	1843	305	0,5	8,7
n	6	6	6	6	6
min	1405	1669	180	0,5	5,3
max	3771	4073	797	1,5	10,5
Median	2377,5	2549	418,5	0,5	7,1
Mean	2481,2	2688,5	422,2	0,8	7,5
St. Dev.	1032,7	1044,3	240,4	0,4	1,9
Geom. Mean	2298,2	2519,3	364,8	0,7	7,3

**Table 4.2.1.7. Absolute Bioavailability of Intranasal Ketorolac Spray (Study # REC-1993-01)**

	Formulation	Treatment	Dose (mg)	Spray Solution Concentration	Mean AUC (*) (ng·h/mL)	Mean Cmax (*) (ng/mL)	AUC ratio	Cmax ratio	F%
Group 1 Subjects N° 1 - 6	I.V. solution	C	10	-	3144,5	-	-	-	-
	B1	A	10	5%	2693,4	-	0,86	-	86
	B2	B	30	15%	5252,5	-	0,58 (§)	-	56
Group 2 Subjects N° 7 - 12	A	A	10	5%	2786,0	502,1	-	-	-
	B1	B	10	5%	2701,6	541,2	0,98	1,08	98
	C	C	10	5%	2519,3	364,8	0,91	0,73	91

(\*) Geometric Mean  
(§) Dose corrected

	Formulation	Treatment : Dose administered - ( formulation with Lot N° )	
Subjects N° 1 - 6	I.V. solution	C : ketorolac tromethamine 10 mg - ( ampoules Lot N° 371/17 )	
	B1	A : ketorolac tromethamine 10 mg - ( 5% spray solution B1 - Lot N° 429/80 )	(b) (4)
	B2	B : ketorolac tromethamine 30 mg - ( 15% spray solution B2 - Lot N° 429/84 )	
Subjects N° 7 - 12	A	A : ketorolac tromethamine 10 mg - ( 5% spray solution A - Lot N° 429/78 )	(b) (4)
	B1	B : ketorolac tromethamine 10 mg - ( 5% spray solution B1 - Lot N° 429/80 )	
	C	C : ketorolac tromethamine 10 mg - ( 5% spray solution C - Lot N° 429/82 )	

**Conclusions:**

From this pilot study, it can be concluded that the ketorolac is sufficiently absorbed after intranasal administration. The absolute bioavailability appears to be in the range of approximately 60% to 85%. There is trend of less than dose proportional increase in exposure as demonstrated for both Cmax and AUC. The (b) (4) do not to show any significant effect on the absorption of the drug after nasal administration.

#### 4.2.2 Study # ROX-2001-01 (Dose Escalation, Proof of Concept):

**Objectives:** The primary object is to compare the PK profiles of single 20, 30, and 40 mg doses of intranasal ketorolac following intranasal administration of 10%, 15%, and 20% solutions. The secondary objective is to determine the effect of the [REDACTED] (b) (4).

#### Study Design:

The study consists two parts of sequential ascending single doses in 9 healthy subjects administered in weekly intervals as follows:

#### Part 1 (Dose Selection Arm)

Week 1: Single intranasal dose of 20 mg of 10% solution (2 x 100 µL in each nostril)  
Week 2: Single intranasal dose of 30 mg of 20% solution (2 x 100 µL in each nostril)  
Week 3: Single intranasal dose of 40 mg of 30 % solution (2 x 100 µL in each nostril)

#### Part II [REDACTED] (b) (4)

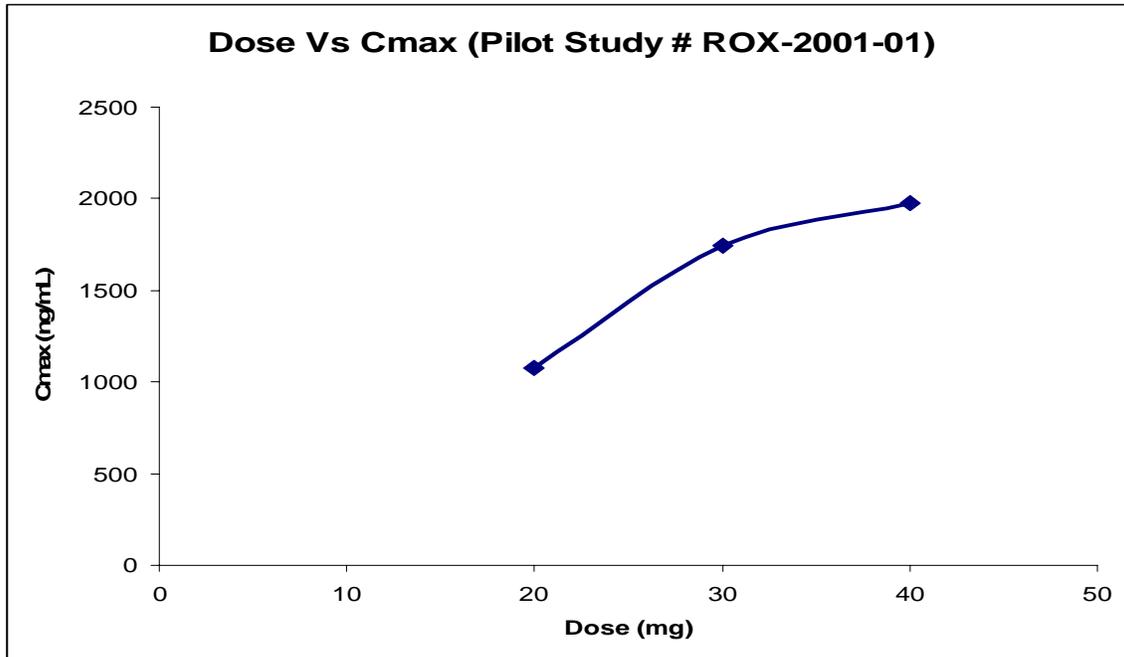
- 30 mg of 15% solution with 0.3% [REDACTED] (b) (4).

Blood was collected over 24 hours.

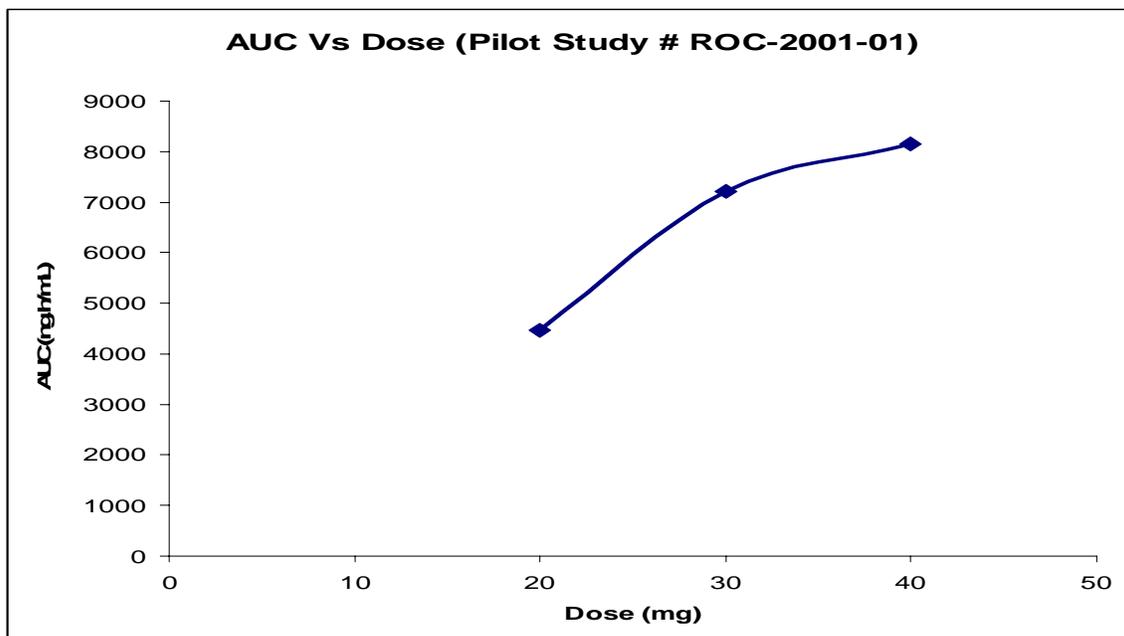
#### Results:

There was less than proportional increase in both C<sub>max</sub> and AUC with increase in ketorolac intranasal dose (**Figures 4.2.2.1-2 and Table 4.2.2.1**). The exposure appears to be dose proportional only between 20 mg and 30 mg doses.

**Figure 4.2.2.1 Dose and Cmax Relationship After Intranasal Administration of Ketorolac Spray (Pilot Study # ROX-2001-01)**



**Figure 4.2.2.2 Dose and AUC Relationship After Intranasal Administration of Ketorolac Spray (Pilot Study # ROX-2001-01)**



Treatment	Mean ( $\pm$ SE) Pharmacokinetic Parameters							
	C <sub>max</sub> (ng/ml)	t <sub>max</sub> (h) <sup>a</sup>	AUC <sub>t</sub> (ng·h/ml)	AUC <sub>inf</sub> (ng·h/ml)	% Extrap	$\lambda_z$ (h <sup>-1</sup> )	t <sub>1/2</sub> (h)	MRT (h)
20 mg ketorolac tromethamine (10 % Solution)	1074.26 (119.41)	0.50 (0.25 - 1.00)	4212.89 (465.92)	4476.74 (448.48)	7 (1)	0.1408 (0.0157)	5.72 (0.64)	7.16 (0.75)
30 mg ketorolac tromethamine (15 % Solution)	1740.71 (190.75)	0.75 (0.25 - 1.00)	6830.91 (698.02)	7215.12 (726.39)	5 (1)	0.1216 (0.0048)	5.82 (0.23)	6.65 (0.30)
40 mg ketorolac tromethamine (20 % Solution)	1977.81 (296.79)	0.52 (0.50 - 1.05)	7626.22 (875.79)	8151.53 (904.19)	7 (1)	0.1173 (0.0071)	6.19 (0.34)	7.59 (0.39)
30 mg ketorolac tromethamine (15 % Solution) plus 0.3 % Sodium Glycocholate	1662.39 (188.79)	0.75 (0.25 - 1.00)	6515.39 (607.30)	6889.28 (616.08)	6 (1)	0.1143 (0.0054)	6.28 (0.35)	7.12 (0.53)

<sup>a</sup> Median and range reported

Based on these data the sponsor selected 30 mg dose for further testing. As shown in **Table 4.2.2.1** there was no noticeable effect of the (b) (4) on either the C<sub>max</sub> or the AUC.

### Conclusions:

It appears that the drug is dose proportional up to 30 mg dose for the solution strength of 15%. Overall, the exposure increases with increase in dose, irrespective of the solution strength. (b) (4).

#### 4.2.3 Study # ROX-2001-02 (Pivotal Single Dose Intranasal vs IM, Dose Selection):

**Objectives:** The object is to compare the PK profiles of single 15, 30, and 45 mg doses of ketorolac administered by intranasal route with 15 mg and 30 mg administered by intramuscular (IM) route.

##### **Study Design:**

This is a single dose 5-way crossover study in 15 healthy subjects with a washout period of one week between treatments as follows:

**Treatment A:** Single dose 15 mg IM (0.5 mL of 30 mg/mL injection solution)

**Treatment B:** Single intranasal dose of 15 mg (equivalent of 15.5 mg) of 7.5% solution (2 x 100 µL in each nostril)

**Treatment C:** Single intranasal dose of 30 mg (equivalent of 31.5 mg) of 15 % solution (2 x 100 µL in each nostril)

**Treatment D:** Single intranasal dose of 45 mg (equivalent of 48 mg) of 22.5 % solution (2 x 100 µL in each nostril)

**Treatment E:** Single dose 30 mg IM (1 mL of 30 mg/mL injection solution)

Blood was collected over 24 hours.

##### **Results:**

- There was less than proportional increase in both C<sub>max</sub> and AUC with increase in ketorolac intranasal dose (**Figures 4.2.3.1 A-C and 4.2.3.2-3 and Table 4.2.3.1**).
- The exposure (C<sub>max</sub> and AUC) appears to be dose proportional only between 15 mg and 30 mg doses administered via IN and IM routes (**Table 4.2.3.1 and Figures 4.2.3.2 to 4.2.3.5**).
- Statistical analysis shows the 90% CI among all treatments is outside the 80% to 125% (**Tables 4.2.3.2 and 3**).
- The bioavailability of intranasal (IN) doses of 15 and 30 mg relative to 15 mg and 30 mg IM was approximately 73% and 60%, respectively.

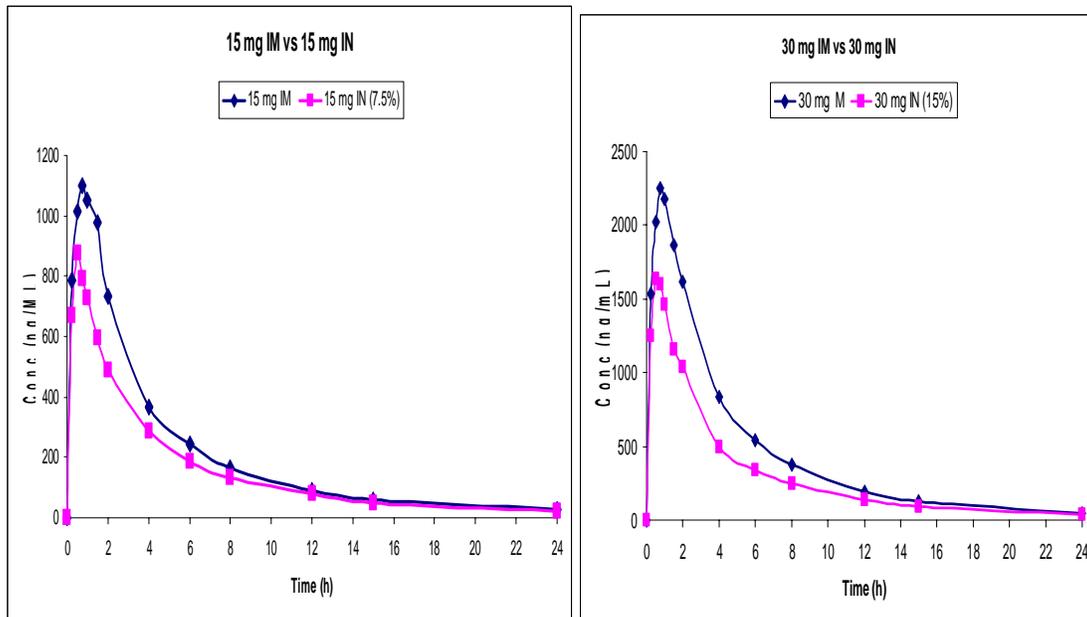
**Table 4.2.3.1 Mean ( $\pm$  SD) PK Parameters Following Intranasal and Intramuscular Ketorolac in Healthy Subjects (Study # ROX-2001-02)**

Ketorolac Treatment	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h) <sup>a</sup>	AUC <sub>0-1</sub> (ng·h/mL)	AUC <sub>0-∞</sub> (ng·h/mL)	t <sub>1/2</sub> (h)	MRT (h)
15 mg IM (0.5 mL of 30 mg/mL)	1163.4 (279.9)	0.75 (0.25-1.50)	4955.6 (1920.5)	5196.3 (2076.7)	5.00 (1.72)	5.79 (1.70)
15.5 mg IN (7.5% Solution)	912.6 (292.9)	0.50 (0.25-1.00)	3723.1 (1483.3)	3906.8 (1569.4)	4.76 (1.38)	5.96 (2.07)
31.5 mg IN (15% Solution)	1805.8 (882.8)	0.75 (0.50-2.00)	7141.1 (3465.8)	7477.3 (3654.4)	5.24 (1.33)	6.31 (2.45)
48 mg IN (22.5% Solution)	2245.5 (1240.4)	0.50 (0.25-1.02)	8246.8 (3106.4)	8669.7 (3173.4)	5.73 (2.03)	6.53 (2.19)
30 mg IM (1.0 mL of 30 mg/mL)	2382.2 (432.7)	0.75 (0.25-1.03)	10770.3 (3885.5)	11152.8 (4260.1)	4.80 (1.18)	5.51 (1.48)

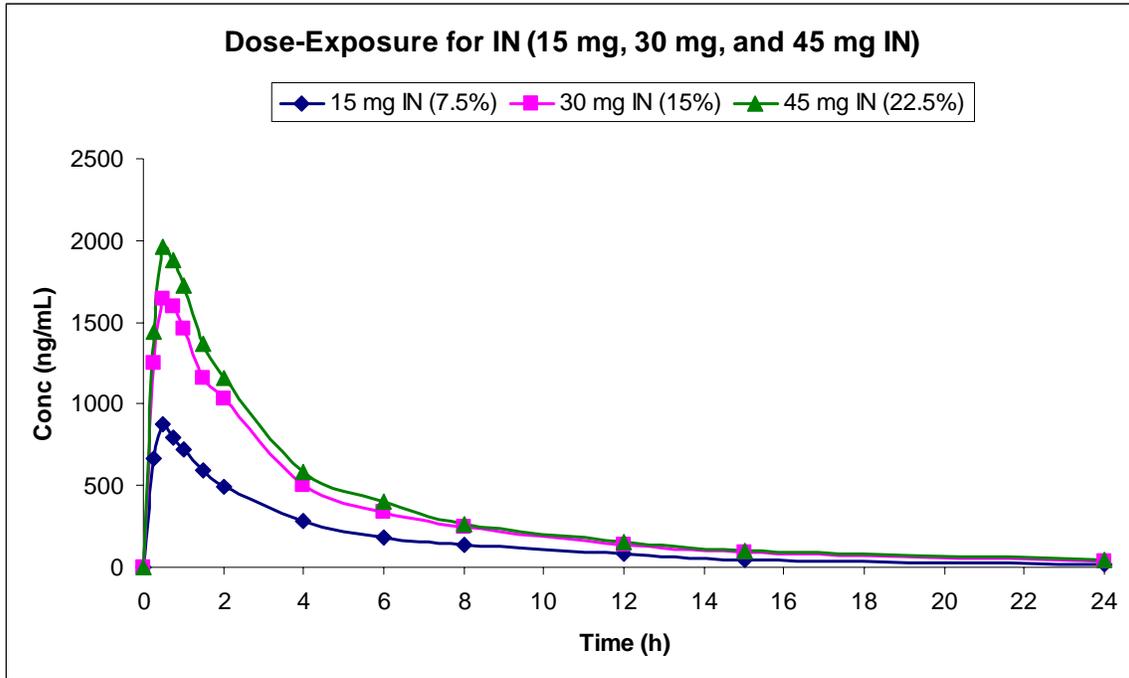
<sup>a</sup> Median and range reported

**Figure 4.2.3.1 A-C. Mean of Ketorolac Plasma Concentration-Time Profiles After Intramuscular (IM) Administration of 15 mg and 30 mg and Intranasal (IN) Administration of 15.5 mg, 31.5 mg, and 48 mg (Study # ROX-2001-002)**

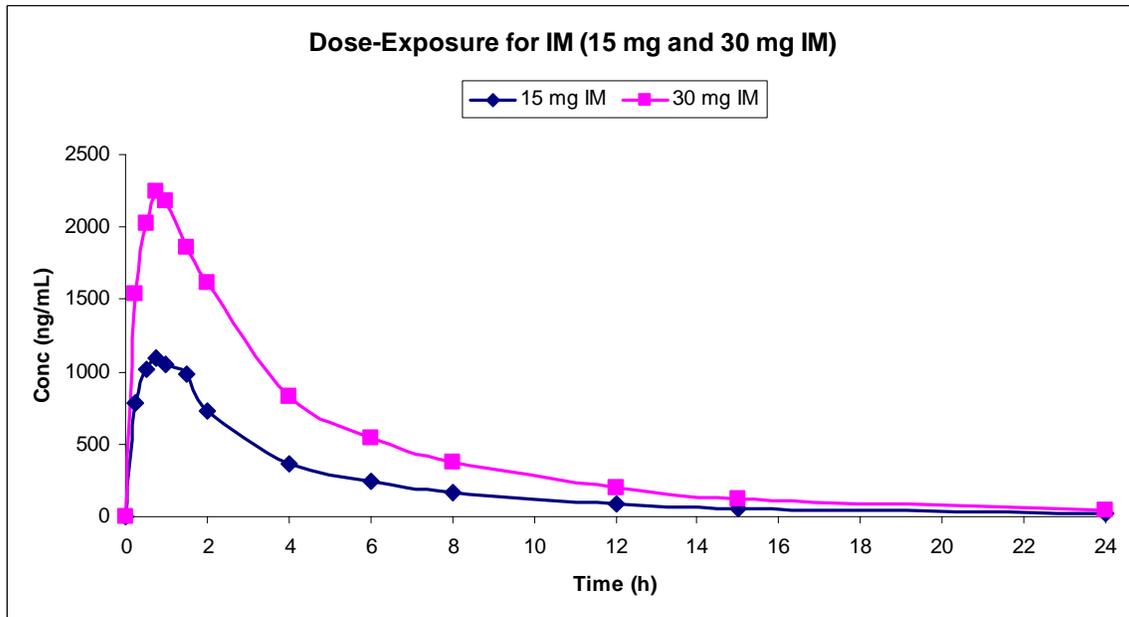
**Figure 1 A. Intramuscular (IM) vs. Intranasal (IN)**



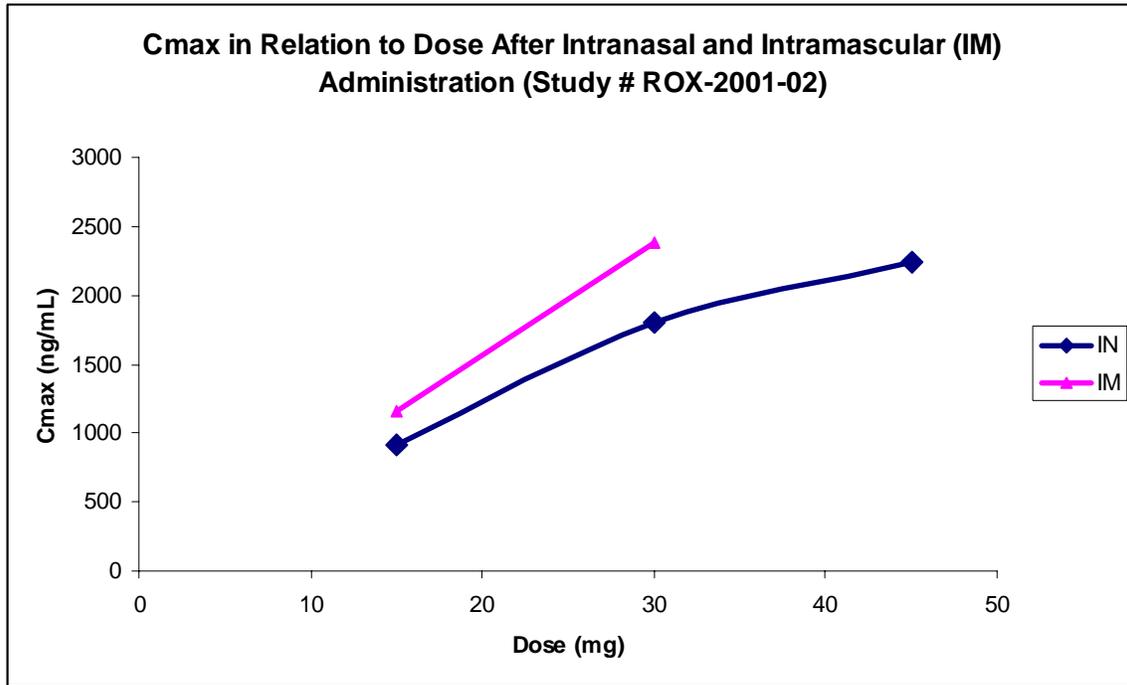
**Figure 4.2.3.1 B. Dose Proportionality for Intranasal Administration**



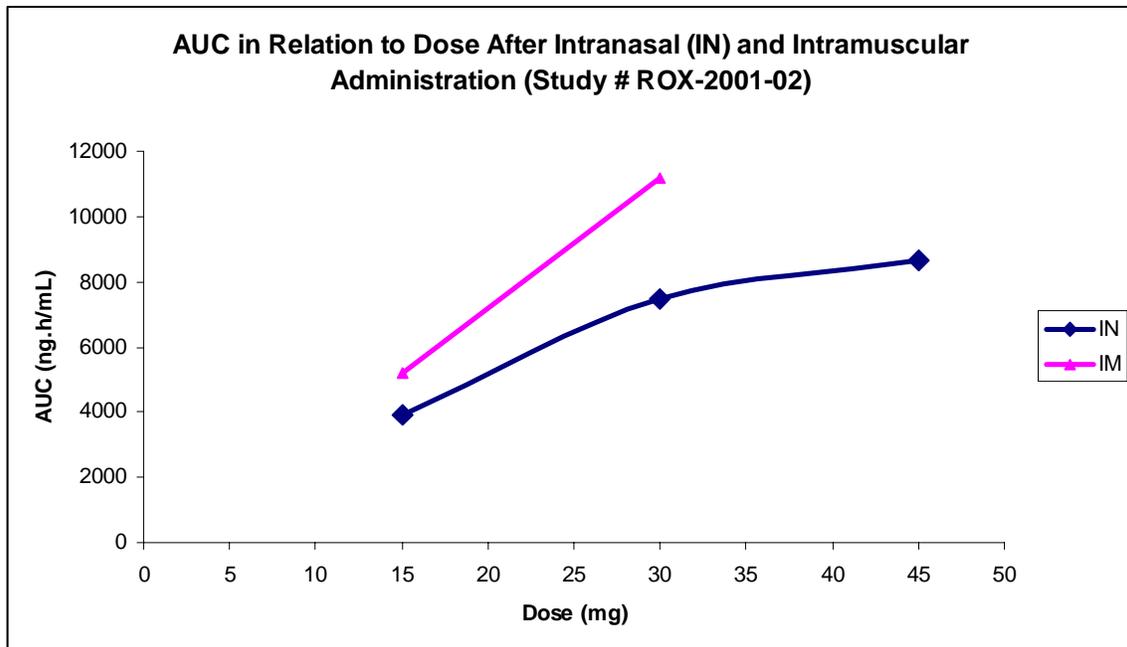
**Figure 4.2.3.1 C. Dose Proportionality for Intramuscular Administration**



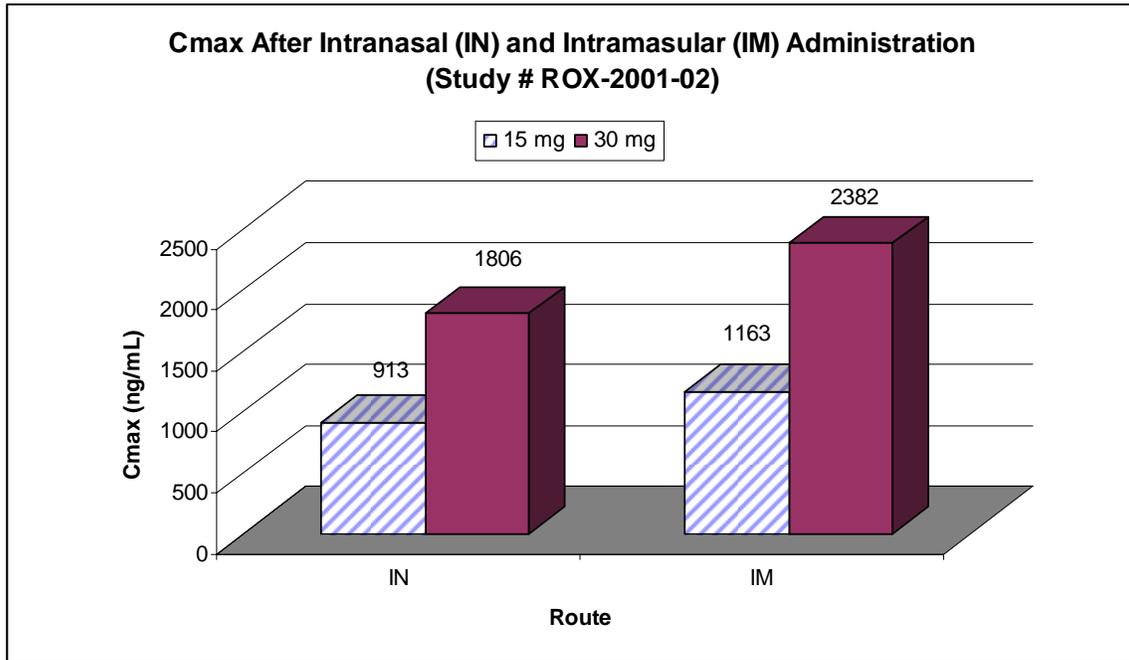
**Figure 4.2.3.2 Mean of Ketorolac Cmax After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**



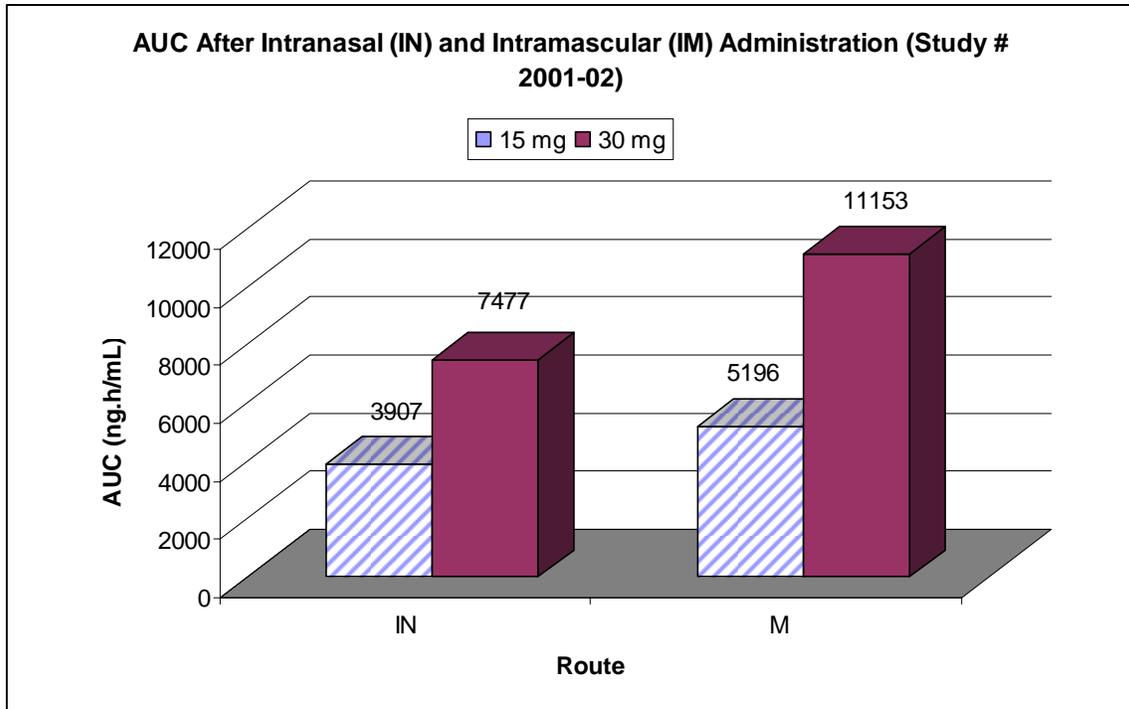
**Figure 4.2.3.3 Mean of Ketorolac AUC<sub>(0-inf)</sub> After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**



**Figure 4.2.3.4 Mean of Ketorolac C<sub>max</sub> After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**



**Figure 4.2.3.5 Mean of Ketorolac AUC<sub>(0-inf)</sub> After Intramuscular and Intranasal Administration (Study # ROX-2001-002)**



**Table 4.2.3.2. Statistical Summary Using ANOVA analysis of Dose-Route Comparisons (Study # ROX-2001-02)**

Parameter	Comparison	Geometric Mean		Point Estimate (%)	90% CI after Tukey Adjustment	
		Test	Reference		Lower	Upper
C <sub>max</sub>	B v A	1670.23	2262.51	73.82	52.56	103.68
	C v A	1433.39	2262.51	63.35	45.11	88.98
	D v A	1241.43	2262.51	54.87	39.07	77.06
	B v E	1670.23	2343.54	71.27	50.75	100.09
	C v E	1433.39	2343.54	61.16	43.55	85.90
	D v E	1241.43	2343.54	52.97	37.72	74.40
AUC <sub>0-1</sub>	B v A	6632.87	9147.25	72.51	58.11	90.49
	C v A	6027.50	9147.25	65.89	52.80	82.23
	D v A	4848.63	9147.25	53.01	42.48	66.15
	B v E	6632.87	10181.2	65.15	52.21	81.30
	C v E	6027.50	10181.2	59.20	47.44	73.88
	D v E	4848.63	10181.2	47.62	38.16	59.43
AUC <sub>0-∞</sub>	B v A	6947.72	9561.16	72.67	58.51	90.25
	C v A	6322.81	9561.16	66.13	53.25	82.13
	D v A	5108.07	9561.16	53.43	43.02	66.35
	B v E	6947.72	10493.9	66.21	53.31	82.23
	C v E	6322.81	10493.9	60.25	48.51	74.83
	D v E	5108.07	10493.9	48.68	39.19	60.45

A = 15 mg IM; B = 15.5 mg IN (7.5% solution); C = 31.5 mg IN (15% solution);  
D = 48 mg IN (22.5% solution); E = 30 mg IM

**Table 4.2.3.2. Statistical Summary Using Non-Parametric Analysis of Dose-Route Comparisons (Study # ROX-2001-02)**

Parameter	Treatment Comparison	Median		Hodges-Lehmann Estimator for Difference in Location	90% CI		p-value
		Test	Ref		Lower	Upper	
t <sub>max</sub>	B v A	0.500	0.750	-0.125	-0.260	0.000	0.1431
	C v A	0.750	0.750	0.125	-0.125	0.250	0.3439
	D v A	0.500	0.750	-0.010	-0.250	0.125	0.6421
	B v E	0.500	0.750	-0.250	-0.375	-0.115	0.0193
	C v E	0.750	0.750	-0.013	-0.230	0.250	0.8634
	D v E	0.500	0.750	-0.125	-0.260	0.020	0.2876

Ref = reference

A = 15 mg IM; B = 15.5 mg IN (7.5% solution); C = 31.5 mg IN (15% solution);

D = 48 mg IN (22.5% solution); E = 30 mg IM

Data source: Appendix 16.2.10.5 and 16.2.10.6

**Conclusions:**

- It appears that the drug is dose proportional up to 30 mg dose IM and IN. However, above 30 mg the exposure (C<sub>max</sub> and AUC) is less than dose proportional.
- None of the IN treatments were bioequivalent to IM route at any dose.
- The relative bioavailability of IN route to IM route was approximately 73% after 15 mg dose and 60% after 30 mg dose.

#### 4.2.4 Study # ROX-2001-04 (Multiple Doses Intranasal X 5 Days, Placebo Controlled):

**Objectives:** The primary objectives are to compare the safety of 5 days multiple doses intranasal administration to placebo and to determine steady-state level.

#### Study Design:

Multiple dose, double-blind, placebo controlled, parallel group, four times daily 30 mg doses for 5 days in 18 healthy subjects as follows:

#### Day-1:

- Physical examination, including nasal cavity

#### Day 1:

- Subjects were dosed four times daily (every 6 hours) with 30 mg doses of ketorolac (15% solution) or matched placebo until morning of Day 6.
- 12 subjects receive active treatments and 6 subjects received placebo.
- Evaluation performed daily

#### Day 6:

- Physical examination including nasal cavity
- PK blood samples were collected prior to the last dose and at 0.5, 1, 2, 4, and 6 hours after the last dose.

#### Results:

- On Day 6, the mean C<sub>max</sub> was 1657 ng/ml and the AUC<sub>0-6h</sub> was 5442 ng·h/mL (Table 4.2.4.1 and 4.2.4.2 and Figure 4.2.4.1). There was wide variability in the as shown in the individual plasma concentration time profiles (Figure 4.2.4.2).
- According to the physical examination, most of the side effects were related to irritation to the nasal cavity due to ketorolac compared placebo.

**Table 4.2.4.1 Mean (± SD) PK Parameters on Day 6 (Study # ROX-2001-04)**

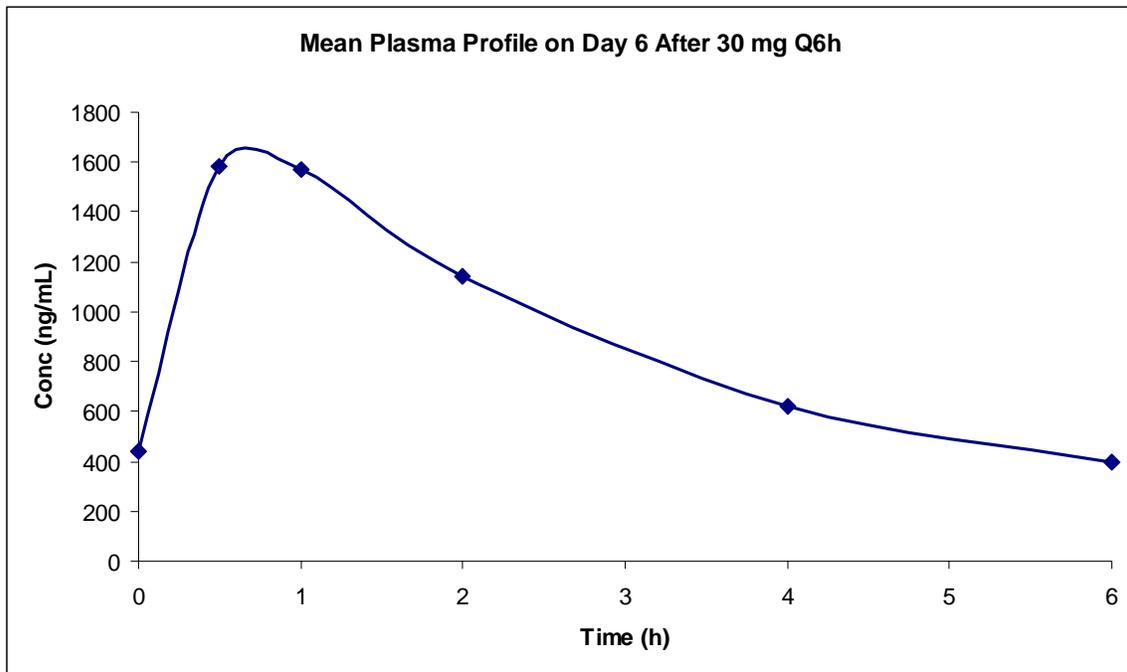
C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h) <sup>*</sup>	AUC <sub>0-6h</sub> (ng·h/mL)	MRT (h)
1657.86 (±809.16)	1.00 (0.50-1.00)	5442.26 (±2809.26)	2.25 (±0.17)

<sup>\*</sup> Median and range reported

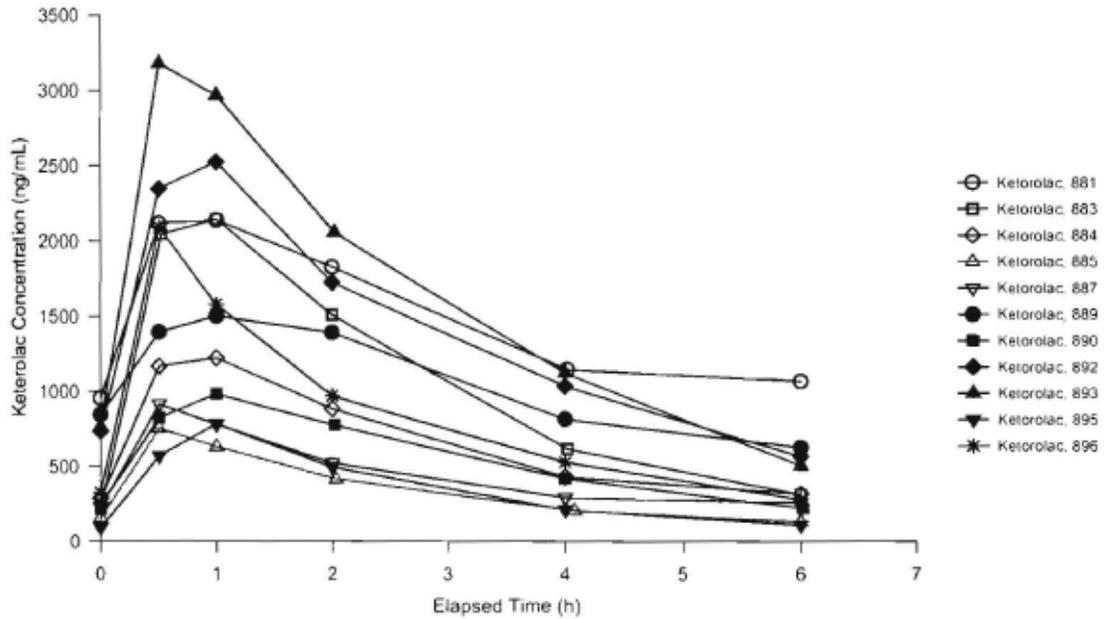
**Table 4.2.4.2 Individual and Mean PK Parameters on Day 6 (Study # ROX-2001-04)**

Subject Number	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	AUC <sub>0-6h</sub> (ng·h/mL)	MRT (h)
881	2139.72	1.00	9017.06	2.58
883	2145.08	1.00	6494.03	2.08
884	1221.18	1.00	4080.42	2.26
885	752.46	0.50	2078.55	2.12
887	914.15	0.50	2731.05	2.30
889	1500.45	1.00	6382.84	2.50
890	981.65	1.00	3447.75	2.32
892	2525.18	1.00	8480.39	2.28
893	3182.18	0.50	9872.98	2.16
895	781.79	1.00	2174.79	2.11
896	2092.57	0.50	5105.03	2.06
N	11	11	11	11
Mean	1657.86		5442.26	2.25
SD	809.16		2809.26	0.17
SE	243.97		847.02	0.05
Min	752.46	0.50	2078.55	2.06
Median	1500.45	1.00	5105.03	2.26
Max	3182.18	1.00	9872.98	2.58
CV%	48.81		51.62	7.55
95% CI Lower	1114.25		3554.97	2.14
95% CI Upper	2201.46		7329.55	2.37

**Figure 4.2.4.1 Mean Plasma Concentration-Time Profile of Ketorolac on Day 6 (Study # ROX-2001-04)**



**Figure 4.2.4.2 Individual Subjects Plasma Concentration-Time Profile of Ketorolac on Day 6 (Study # ROX-2001-04)**



**Conclusions:**

- From this study it can be concluded that the C<sub>max</sub> of ketorolac occurs within 1 hour of intranasal administration. The concentration at pre-dose on Day 6 following 5 days QID administration is approximately comparable to the concentration at 6 hours. This suggests that the steady state has been achieved.

#### 4.2.5 Study # ROX-2005-03 (Multiple Doses Intranasal X 3 Days):

**Objectives:** The primary objectives are to determine the safety of 3 days multiple doses intranasal administration and the PK profiles after 3 days of TID (Q8h) administration.

##### **Study Design:**

This is multiple dose, open label, three times daily (Q8h) of 30 mg doses for 3 days in 15 healthy subjects (seven doses total). Subjects receive each intranasal dose as 100 µL spray of 15% solution in each nostril.

The PK blood samples were collected prior each dose (for trough level determination) and every hour for eight hours post dose on Day 1 and 3 (morning dose).

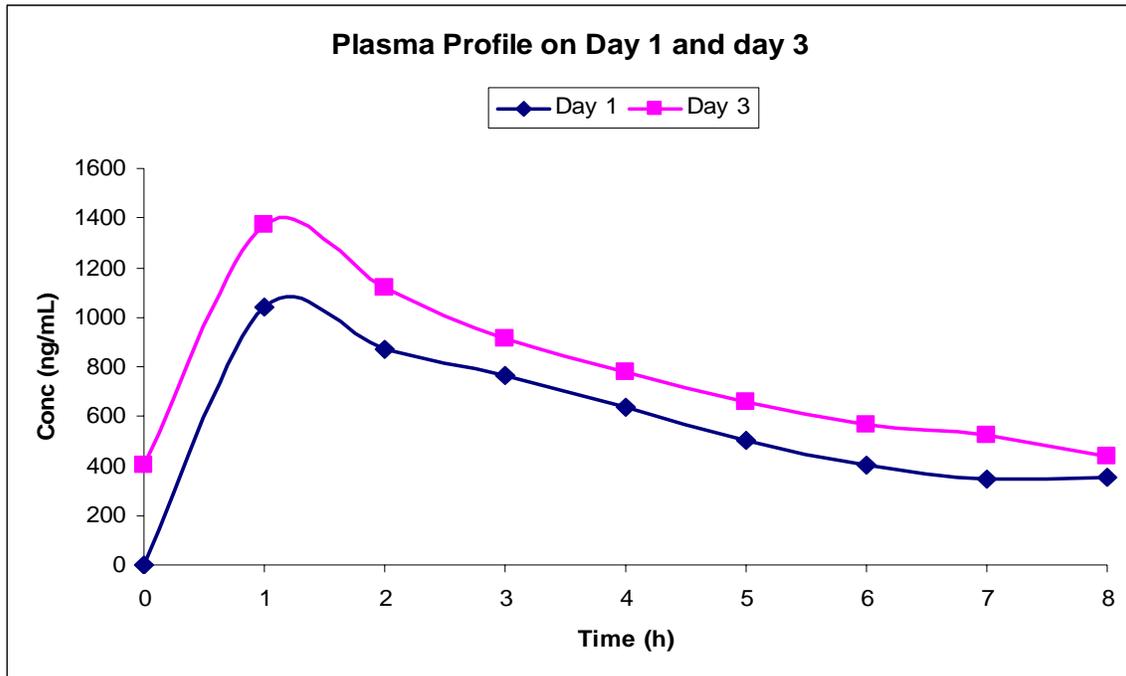
##### **Results:**

- The mean C<sub>max</sub> on Day 1 was approximately 1148 ng/mL and on Day 3 was approximately 1800 ng/mL (**Tables 4.2.5.1**). The individual data is shown in **Tables 4.2.5.2 and 4.2.5.3**.
- The mean AUC<sub>(0-8h)</sub> on Day 1 was 4714 ng/ml and on Day 3 was 6380 ng.h/mL. The plasma concentration-time profiles on Day 1 and Day 3 shows evidence of accumulation of ketorolac (**Figure 4.2.5.1 A and B**). The exposure on Day 3 is approximately 40% higher than on Day 1.
- Steady state concentration appears to achieved by 24 hours.
- Most of the observed side effects are related to nasal discomfort.

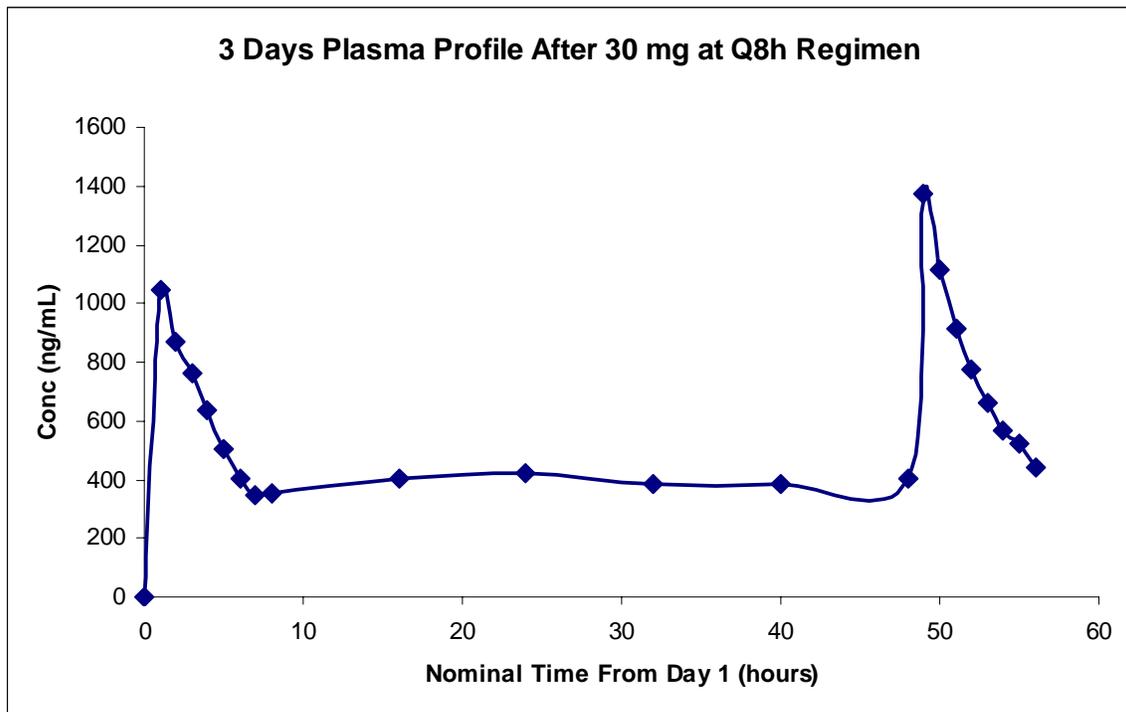
**Table 4.2.5.1 Summary of Ketorolac PK Parameters on Day 1 and Day 3 (Study # ROX-2005-03)**

Day	Parameter	Summary Statistic	30 mg Ketorolac tromethamine i.n. t.i.d.
Number of subjects receiving treatment			15
Day 1	C <sub>max</sub> (ng/mL)	n	13
		Mean	1147.9
		SE	186.0
	T <sub>max</sub> (h)	n	13
		Median	1.000
		Range	1.00 – 7.92
	AUC <sub>0-8h</sub> (ng·h/mL)	n	13
		Mean	4713.8
		SE	744.8
Day 3	C <sub>max,ss</sub> (ng/mL)	n	13
		Mean	1382.6
		SE	224.3
	T <sub>max,ss</sub> (h)	n	13
		Median	1.000
		Range	1.00 – 3.00
	C <sub>min,ss</sub> (ng/mL)	n	13
		Mean	367.7
		SE	67.7
	T <sub>min,ss</sub> (h)	n	13
		Median	0.000
		Range	0.00 - 8.00
	AUC <sub>τ</sub> (ng·h/mL)	n	13
		Mean	6379.2
		SE	1031.0
	MRT (h)	n	13
		Mean	3.368
		SE	0.056
	PTF	n	13
		Mean	1.222
		SE	0.052
Rac	n	13	
	Mean	1.561	
	SE	0.174	

**Figure 4.2.5.1 A. Mean Plasma Concentration-Time Profile of Ketorolac on Day 1 and 3 (Study # ROX-2005-03)**



**Figure 4.2.5.1 B. Three Days Profile of ketorolac of 30 mg Dose (Study # ROX-2005-03)**



**Table 4.2.5.2 Individual and Mean PK Parameters on Day 1 (Study # ROX-2005-03)**

Subject	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-8h</sub> (ng·h/mL)
1	1030	1.00	4595
2	2048	1.00	8209
3	939	1.00	4674
4	608	1.00	2518
5 <sup>2</sup>	NC	NC	NC
6	1544	1.00	7326
7	900	7.92	3984
8	374	1.00	1854
9	1134	1.00	5704
10	2184	1.00	6591
11	301	1.00	1282
12 <sup>2</sup>	173	1.00	504
13	264	1.00	908
14	1761	1.00	4143
15	1835	3.00	9493
n	13	13	13
Arithmetic mean	1147.9		4713.8
SD	670.7		2685.2
SE	186.0		744.8
CV(%)	58.4		57.0
Geometric mean	931.5		3853.4
Geometric CV(%)	83.9		83.4
Lower 95% CI <sup>1</sup>	742.6		3091.1
Upper 95% CI <sup>1</sup>	1553.2		6336.5
Median	1029.8	1.000	4594.7
Minimum	264	1.00	908
Maximum	2184	7.92	9493

**Table 4.2.5.3 Individual and Mean PK Parameters on Day 3 (Study # ROX-2005-03)**

Subject	C <sub>max,ss</sub> (ng/mL)	T <sub>max,ss</sub> (h)	C <sub>min,ss</sub> (ng/mL)	T <sub>min,ss</sub> (h)	AUC <sub>0-8h</sub> (ng·h/mL)	MRT (h)	PTF	Rac
1	1591	1.00	598	8.00	8063	3.48	0.86	1.75
2	3418	1.00	954	0.00	13700	3.34	1.44	1.67
3	1669	1.00	265	0.00	8788	3.66	1.28	1.88
4	875	1.00	150	0.00	4234	3.44	1.35	1.68
5 <sup>2</sup>	267	2.00	123	7.00	1432	3.49	0.72	-
6	1385	1.00	472	7.02	6445	3.36	1.25	0.88
7	1434	1.00	451	8.00	6631	3.43	1.19	1.66
8	862	1.00	237	8.00	3606	3.24	1.14	1.94
9	1091	2.00	231	0.00	4832	3.25	1.42	0.85
10	1287	1.00	195	8.00	4619	2.87	1.53	0.70
11	611	3.00	223	0.00	3142	3.55	0.99	2.45
12 <sup>2</sup>	185	1.00	66	0.00	880	3.43	1.07	1.74
13	565	1.00	131	8.00	2419	3.18	1.10	2.67
14	699	1.00	213	0.00	3090	3.38	1.26	0.75
15	2488	1.00	652	0.00	13361	3.57	1.10	1.41
n	13	13	13	13	13	13	13	13
Arithmetic mean	1382.6		367.7		6379.2	3.368	1.222	1.561
SD	808.7		244.2		3717.3	0.203	0.189	0.628
SE	224.3		67.7		1031.0	0.056	0.052	0.174
CV(%)	58.5		66.4		58.3	6.0	15.4	40.3
Geometric mean	1206.3		307.7		5521.7	3.362	1.208	1.433
Geometric CV(%)	57.3		66.5		59.7	6.229	16.150	47.116
Lower 95% CI <sup>1</sup>	894.0		220.1		4132.9	3.245	1.108	1.101
Upper 95% CI <sup>1</sup>	1871.3		515.3		8625.5	3.490	1.336	1.941
Median	1286.9	1.000	237.5	0.000	4831.7	3.380	1.245	1.669
Minimum	565	1.00	131	0.00	2419	2.87	0.86	0.70
Maximum	3418	3.00	954	8.00	13700	3.66	1.53	2.67

**Conclusions:**

- From this study it can be concluded that the C<sub>max</sub> of ketorolac occurs within 1 hour of intranasal administration. The exposure on Day 3 appears to be higher by approximately 40% compared to that on Day 1.
- Steady state is achieved by 24 hours of TID administration.
- The nasal solution was relatively tolerated by all subjects, except with some cases of nasal discomfort after spray.

#### 4.2.6 Study # ROX-2007-02 (PK in Elderly >65 years vs Non-elderly <65 years)

**Objectives:** The primary objective is to compare the PK profiles of intranasal ketorolac between elderly and non-elderly adult subjects.

##### Study Design:

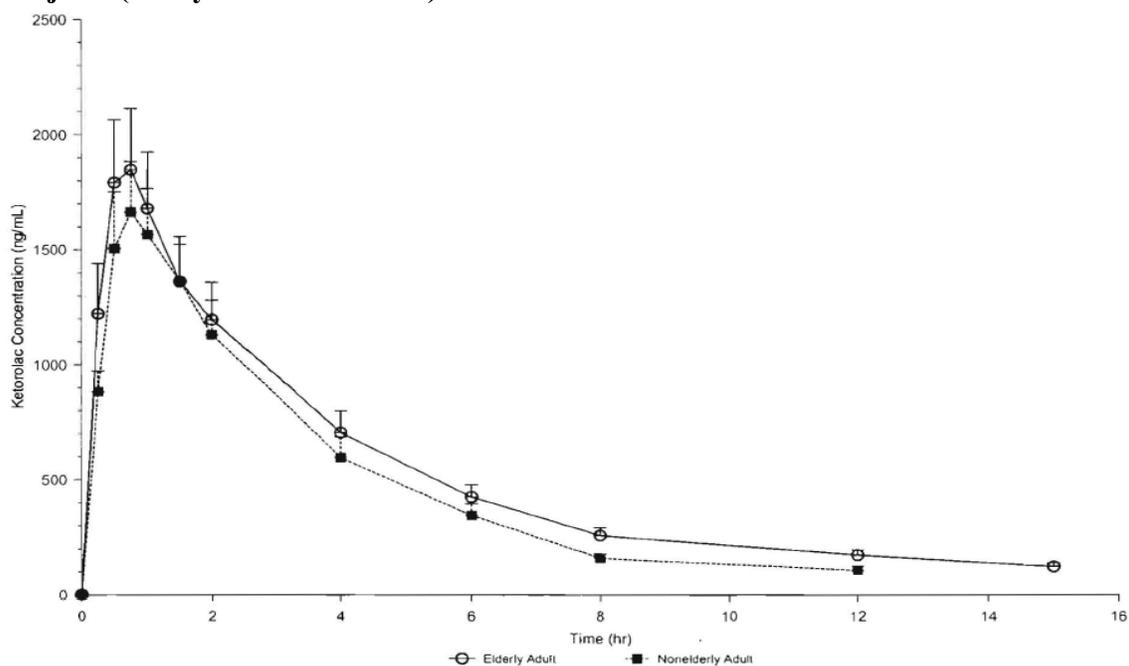
This is a single 30 mg dose study in a total of 30 subjects between ages of 26 and 82 years. Non-elderly group consisted of 15 subjects of <65 years of age with at least 5 subjects under the age of <45 years. The elderly group also consisted of 15 subjects of >65 years of age with at least 5 subjects >75 years. The dose was administered as 100 µl spray in each nostril of 15% solution.

The PK blood samples were collected over 24 hours post administration.

##### Results:

- Overall, the plasma concentration-time profiles in elderly and nonelderly are comparable (**Figure 4.2.6.1**).
- The mean C<sub>max</sub> in elderly was approximately 1780 ng/mL with two outlier subjects and 2028 excluding the outlier subjects. This is comparable to that of the nonelderly subjects with C<sub>max</sub> approximately 1840 ng/mL (**Table 4.2.6.1**).
- The AUC<sub>(0-last)</sub> was slightly higher in elderly (~8000 ng.h/mL) compared to nonelderly (~6500 ng.h/mL) (**Table 4.2.6.1**).

**Figure 4.2.6.1 Mean Plasma Concentration-Time Profiles in Elderly and Nonelderly subjects (Study # ROX-2007-02)**



**Table 4.2.6.1 Summary of Ketorolac PK Parameters in Elderly and Nonelderly Subjects (Study # ROX-2007-02)**

Parameter	Summary Statistic	Population Group		
		Elderly Adults <sup>1</sup>	Elderly Adults	Nonelderly Adults
Number of subjects receiving treatment		15	13	15
$C_{max}$ (ng/mL)	n	15	13	15
	Mean	1782.286	2028.821	1840.111
	SD	1184.843	1069.470	995.930
$T_{max}$ (h)	n	15	13	15
	Median	0.750	0.750	0.750
	Range	0.50 – 1.00	0.50 – 1.00	0.25 – 1.00
$AUC_{last}$ (ng·h/mL)	n	15	13	15
	Mean	7323.5	8344.8	6536.5
	SD	4633.1	4069.8	3361.8
AUC (ng·h/mL)	n	-	13	15
	Mean	-	8794.8	6890.8
	SD	-	4129.4	3448.5
$t_{1/2}$ (h)	n	-	13	15
	Mean	-	4.521	3.313
	SD	-	1.142	0.961
MRT (h)	n	-	13	15
	Mean	-	6.024	4.441
	SD	-	1.496	1.060

**Conclusions:**

Overall, the exposure (AUC) in elderly is approximately 20% higher than nonelderly.

#### 4.2.7 Study # ROX-2006-02 (PK in Children 12 to 17 Years of Age)

**Objective:** The primary objective of this study is to determine the PK of a single intranasal ketorolac dose in pediatric population

##### **Study Design:**

A single intranasal dose of either 15 mg or 30 mg was administered in 20 children 12 to 17 years of age who had undergone general surgery. Dosing for approved ketorolac products consists of half the prescribed dose in patients weighing <50.0 kg. In this study, patients were stratified into two groups based on their body weight. Patients weighing <50.0 kg received 15 mg dose while patients weighing  $\geq 50.0$  kg received 30 mg dose. For the 15 mg dose each subjects received 100  $\mu$ l of 15% solution in only one nostril while for the 30 mg dose was 100  $\mu$ l in each nostril.

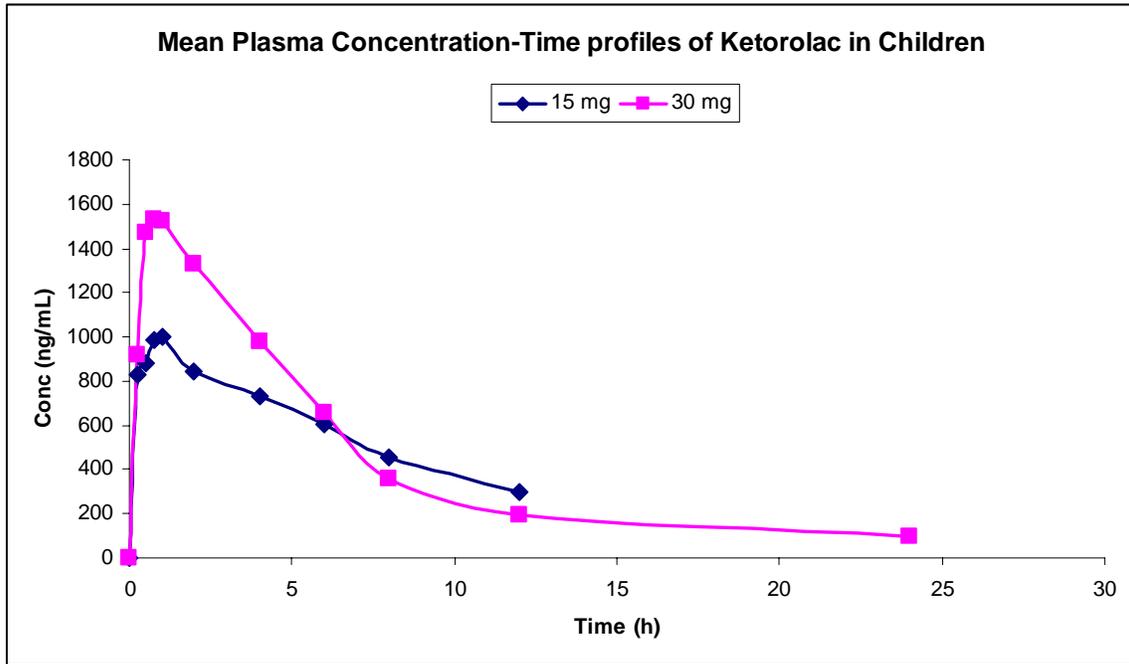
##### **Results:**

- One patient (subject 8) weighing 91 kg refused the second spray and therefore received 15 mg dose instead of the planned 30 mg dose.

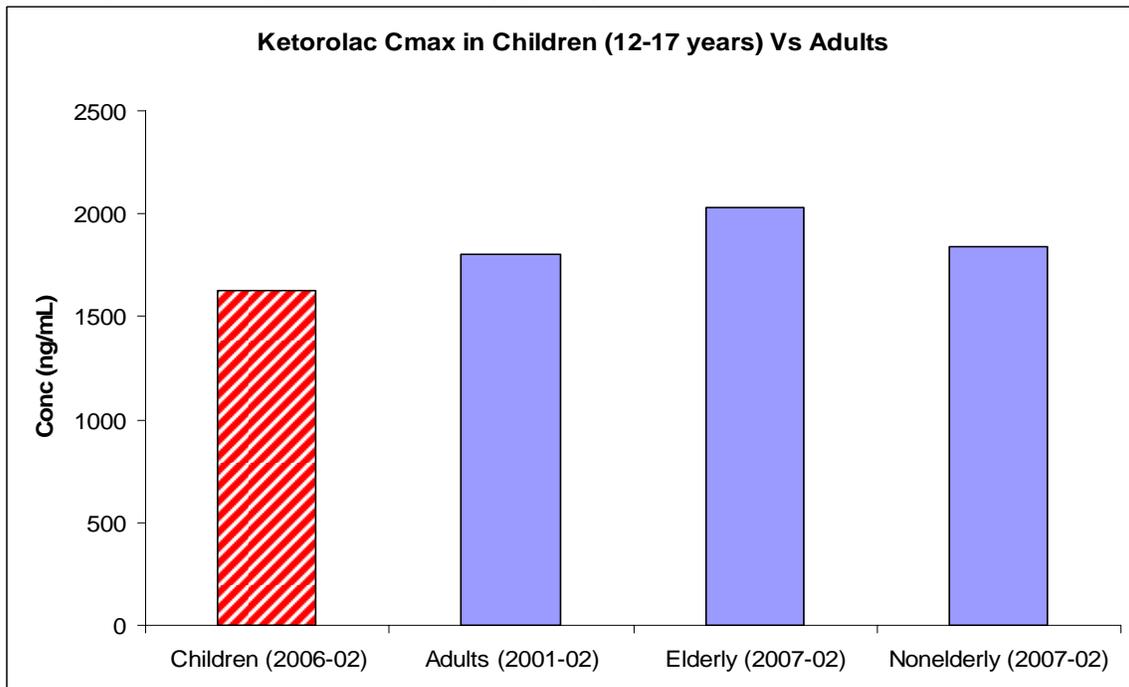
The plasma concentration-time profiles and exposure ( $C_{max}$  and AUC) are shown in **Figure 4.2.7.1 and Table 4.2.7.1**, respectively. The AUC after 30 mg dose (in patients weighing  $\geq 50.0$  kg) was only about 12% higher (10% higher excluding subject 8) than that after 15 mg dose in patients weighing <50.0 kg.

- Overall, considering the variability across studies, the exposure (AUC) in the pediatric population appears to be about 25% higher to that previously obtained from adult subjects receiving a 31.5 mg intranasal dose. (**Figures 4.2.7.2-3**).

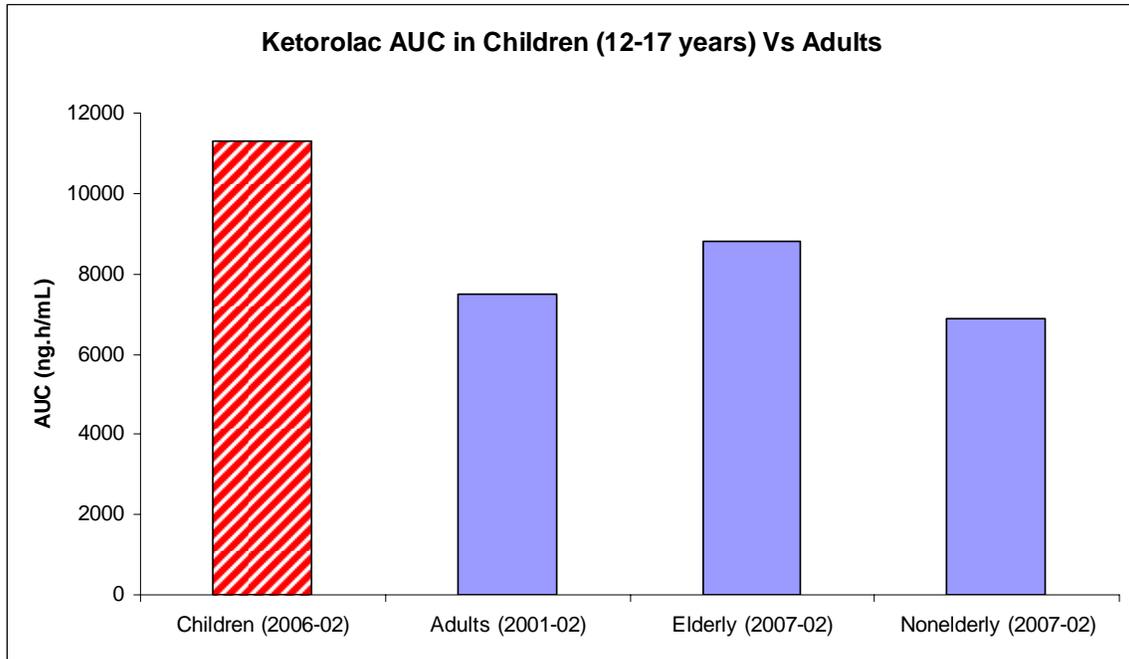
**Figure 4.2.7.1 Figure 2.3.2 Mean Plasma Concentration-Time Profiles of Ketorolac in Pediatric Patients After 15 mg and 30 mg Single Intranasal Doses (Study # ROX-2006-02)**



**Figure 4.2.7.2 Cross Studies Comparison of Mean Ketorolac Cmax Following 30 mg Single Intranasal Dose in Children (Study # ROX 2006-02), adults (Study # ROX 2001-02), and elderly and non-elderly (Study # ROX 2007-02)**



**Figure 4.2.7.3 Cross Studies Comparison of Mean Ketorolac AUC Following 30 mg Single Intranasal Dose in Children (Study # ROX 2006-02), adults (Study # ROX 2001-02), and elderly and non-elderly (Study # ROX 2007-02)**



**Table 4.2.7.1 Summary of Ketorolac PK Data in Pediatric Patients After 15 mg and 30 mg Single Intranasal Doses (Study # ROX-2006-02)**

Parameter	Summary Statistic	Dose Level	
		15 mg IN	30 mg IN
Number of subjects receiving treatment		7	13
$C_{max}$ (ng/mL)	n	7	13
	Mean	1153.896	1625.284
	SD	484.961	538.479
$T_{max}$ (h)	N	7	13
	Median	0.720	0.780
	Range	0.38 – 6.07	0.48 – 5.00
$AUC_{last}$ (ng.h/mL)	N	7	13
	Mean	9308.2	10662.1
	SD	6214.2	5383.5
$AUC$ (ng.h/mL)	N	6	12
	Mean	10590.7	11949.5
	SD	7818.4	6506.1
$AUC_{0-24}$ (ng.h/mL)	N	7	12
	Mean	9600.5	11317.2
	SD	5959.9	5666.1
$t_{1/2}$ (h)	N	6	12
	Mean	6.678	5.031
	SD	2.882	2.055
MRT (h)	N	6	12
	Mean	9.664	6.727
	SD	3.892	1.945

**Conclusions:**

Overall, in the pediatric age group of 12- 17 years, the exposure seems to be about 25% higher (considering the variability across different studies) compared to adults receiving the same dose of 30 mg. .

#### 4.2.8 Study # ROX-2006-03 (Effect of Oxymetazoline Nasal Spray)

**Objective:** The primary objective of this study is to determine the effect of a single dose of intranasal oxymetazoline (Afrazin® in UK = OTC Afrin® in US) on the PK of intranasal ketorolac after a single dose.

##### **Study Design:**

This was two-way crossover study at a single 30 mg ketorolac dose with a washout period of at least 2 days between treatments in 21 healthy subjects. Each subject received a single dose of 30 mg ketorolac (15 mg as 100 µL solution in each nostril) alone or with a single dose (3 sprays in each nostril) of oxymetazoline (Afrazine® = Afrin® in US) as follows:

**Treatment A (Alone):** Single intranasal dose of 30 mg ketorolac (15 mg as 100 µL spray in each nostril)

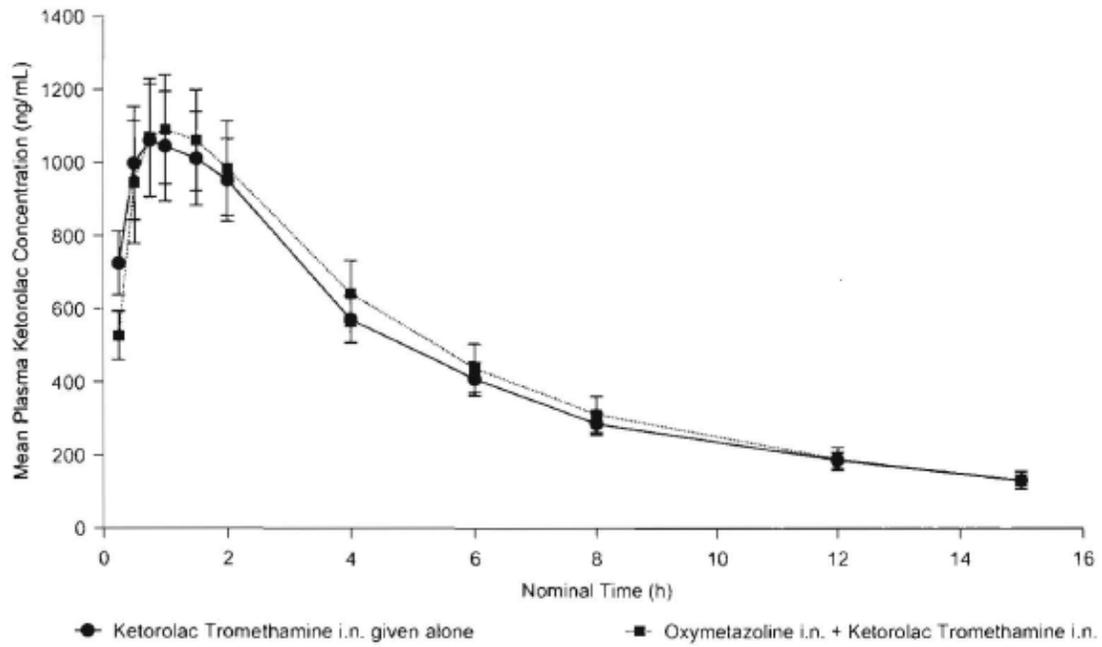
**Treatment B (Combination):** Single intranasal dose of 0.05% solution of oxymetazoline (Afrazine®) as 3 sprays in each nostril followed by intranasal 30 mg ketorolac (as in Treatment A) **30 minutes later.**

Blood samples were collected for PK analysis over 24 hours.

##### **Results:**

- The plasma concentration-time profiles of ketorolac were almost superimposable following the two treatments (**Figures 4.2.8.1**).
- Both the C<sub>max</sub> and AUC were comparable following the two treatments (**Table 4.2.8.1**). However, the 90% CI for both C<sub>max</sub> and AUC were outside 80% and 125% (**Tables 4.2.8.2**). This suggests that the two treatment are not bioequivalent, but comparable

**Figure 4.2.8.1 Mean ( $\pm$  SE) Plasma Concentration-Time Profiles Ketorolac when Given Alone or with oxymetazoline (Study # ROX-2006-03)**



**Table 4.2.8.1 Summary of PK Parameters of Ketorolac When Given Alone or with Oxymetazoline (Study # ROX-2006-03)**

Parameter	Summary Statistic	Treatment	
		A	B
Number of subjects receiving treatment		21	22 <sup>1</sup>
C <sub>max</sub> (ng/mL)	n	21	21
	Mean	1187.870	1281.628
	SD	756.293	842.187
t <sub>max</sub> (h)	n	21	21
	Median	1.000	1.050
	Range	0.42 – 2.00	0.50 – 4.00
AUC <sub>0-t</sub> (ng·h/mL)	n	21	21
	Mean	7343.3	7585.5
	SD	3719.0	4787.7
AUC <sub>inf</sub> (ng·h/mL)	n	21	18 <sup>2</sup>
	Mean	8303.7	9504.0
	SD	4133.0	5136.7
t <sub>1/2</sub> (h)	n	21	18 <sup>2</sup>
	Mean	7.438	6.547
	SD	2.175	2.959
MRT (h)	n	21	18 <sup>2</sup>
	Mean	9.900	8.666
	SD	3.463	3.906

Treatment A = Ketorolac Tromethamine i.n. given alone

Treatment B = Oxymetazoline i.n. + Ketorolac Tromethamine i.n.

<sup>1</sup>One subject excluded from the PK population as they did not complete both study periods

<sup>2</sup>The half-life could not be estimated for 3 subjects due to the nature of their PK profile

**Table 4.2.8.2. Point Estimate and 90% CI for the Treatment Comparison of PK Parameters When Given Alone or with Oxymetazoline (Study # ROX-2006-03)**

Parameter	Test	Reference	n		Geometric LS Mean		Geometric LS Mean	90% CI for Geometric
			Test	Reference	Test	Reference	Ratio	LS Mean Ratio (%)
							(Test/Reference) (%)	[Lower – Upper]
$C_{max}$	B	A	21	21	891.77	950.60	93.81	[64.71 – 136.01]
$AUC_{0-t}$	B	A	21	21	5588.12	6329.57	88.29	[62.48 – 124.75]
$AUC_{inf}^1$	B	A	18	21	8057.55	7282.65	110.64	[88.42 – 138.45]
$AUC_{inf}^2$	B	A	18	18	7973.40	7155.92	111.42	[88.46 – 140.34]

Treatment A = Ketorolac Tromethamine i.n. given alone

Treatment B = Oxymetazoline i.n. + Ketorolac Tromethamine i.n.

<sup>1</sup> $AUC_{inf}$  could not be calculated for Subjects 2, 5 and 9 for Treatment B;  $AUC_{inf}$  for Treatment A for these 3 subjects was included in the statistical analysis.

<sup>2</sup>Subjects 2, 5 and 9 were excluded from the statistical analysis.

### Conclusions:

Considering the variability in the data, it can be concluded that oxymetazoline does not have clinically significant effect of the absorption of intranasal ketorolac when administered 30 min before intranasal ketorolac. However, it is not known if there will be any interaction of the two sprays used simultaneously.

#### 4.2.9 Study # ROX-2006-04 (Effect of Multiple Doses of Fluticasone Propionate in Healthy)

**Objective:** The primary objective of this study is to determine the effect of multiple doses (5 days) of intranasal fluticasone (Flixonase® in UK = Flonase® in US) on the PK of intranasal ketorolac after a single dose.

##### Study Design:

This was two-way crossover study at a single 30 mg ketorolac dose with a washout period of at least 2 days between treatments in 36 healthy subjects. Each subject received a single dose of 30 mg ketorolac (15 mg as 100 µL solution in each nostril) on Days 1 and 6. On Days 2 to 6 subjects received standard dose of 200 µg fluticasone propionate (2 x 50 µg sprays in each nostril). The study design is summarized as follows:

**Treatment A (Day 1, Alone):** Single intranasal dose of 30 mg ketorolac (15 mg as 100 µL spray in each nostril)

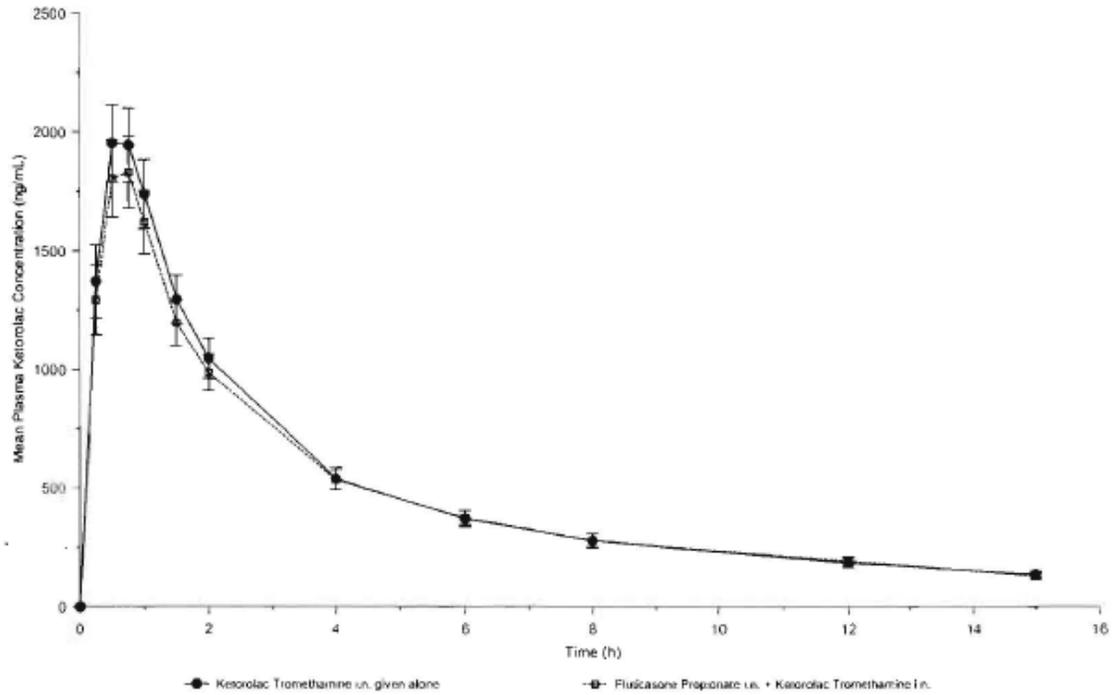
**Treatment B (Combination):** Intranasal 200 µg fluticasone propionate (2 x 50 µg sprays in each nostril) given once per day alone for 5 days (Days 2-6). On Day 6, a single dose of intranasal 30 mg ketorolac was administered (as in Treatment A) **30 minutes** after fluticasone administration **on Day 6 only**.

Blood samples were collected for PK analysis over 24 hours on Day 6 following ketorolac dosing. In addition, trough blood sample was taken on the morning of Day 4

##### Results:

- The plasma concentration-time profiles of ketorolac appears to be superimposable following the two treatments (**Figures 4.2.10.1**). However, it should be noted that the profile is slightly lower when ketorolac is administered with fluticasone than when administered alone.
- Both the C<sub>max</sub> and AUC were comparable following the two treatments (**Table 4.2.9.1**). However, the 90% CI for both C<sub>max</sub> and AUC were outside 80% and 125% (**Tables 4.2.9.2**). This suggests that the two treatment are **not** bioequivalent, but comparable.

**Figure 4.2.9.1 Mean ( $\pm$  SE) Plasma Concentration-Time Profiles Ketorolac when Given Alone on Day 1 or With Fluticasone on Day 6 (Study # ROX-2006-04)**



**Table 4.2.9.1 Summary of PK Parameters of Ketorolac When Given Alone (Day 1) or With Fluticasone on Day 6 (Study # ROX-2006-04)**

Parameter	Summary Statistic	Treatment	
		A	B
Number of subjects receiving treatment		36	36
$C_{max}$ (ng/mL)	n	36	36
	Mean	2128.1	1948.0
	SD	1042.5	1018.3
$t_{max}$ (h)	n	36	36
	Median	0.750	0.750
	Range	0.25 – 1.00	0.25 – 1.00
$AUC_{0-4}$ (ng·h/mL)	n	36	36
	Mean	7991.4	7609.5
	SD	4364.2	4076.8
$AUC_{inf}$ (ng·h/mL)	n	35	36
	Mean	8970.1	8275.5
	SD	4575.7	4380.7
$t_{1/2}$ (h)	n	35	36
	Mean	5.945	5.485
	SD	2.105	2.004
MRT (h)	n	35	36
	Mean	7.049	6.525
	SD	2.141	2.354

Data source: Section 14.3.3

Treatment A = Ketorolac Tromethamine i.n. given alone

Treatment B = Fluticasone Propionate i.n. + Ketorolac Tromethamine i.n.

**Table 4.2.9.2. Point Estimate and 90% CI for the Treatment Comparison of PK Parameters When Given Alone on Day 1 or With Fluticasone on Day 6 (Study # ROX-2006-04)**

Parameter	Test	Reference	n		Geometric LS Mean		Geometric LS Mean Ratio (Test/Reference) (%)	90% CI for Geometric LS Mean Ratio (%) [Lower – Upper]
			Test	Reference	Test	Reference		
$C_{max}$	B	A	36	36	1645.87	1723.65	95.49	[71.32 – 127.84]
$AUC_{0-t}$	B	A	36	36	6212.68	6488.92	95.74	[71.01 – 129.09]
$AUC_{inf}^1$	B	A	36	35	6843.53	7728.05	88.55	[68.14 – 115.08]
$AUC_{inf}^2$	B	A	35	35	6846.81	7728.05	88.60	[67.92 – 115.57]

Data source: Section 14.4.1 and Appendix 16.2.9.1

Treatment A = Ketorolac Tromethamine i.n. given alone

Treatment B = Fluticasone propionate i.n. + ketorolac tromethamine i.n.

<sup>1</sup> $AUC_{inf}$  could not be calculated for Subject 6 Treatment A.

<sup>2</sup> $AUC_{inf}$  could not be calculated for subject 6 Treatment A.  $AUC_{inf}$  for Subject 6 was excluded for both treatments.

### Conclusions:

Considering the variability in the data, it can be concluded that fluticasone do not appear to have clinically significant effect on the absorption of intranasal ketorolac.

#### **4.2.10 Study # ROX-2007-03 (Effect of Oxymetazoline (Drixine® in Australia = Afrin® in US) and Fluticasone Propionate (Beconase® in Australia = Flonase® in US) Sprays on Intranasal Ketorolac in Patients with Allergic Rhinitis)**

##### **Objectives:**

- PK in of intranasal ketorolac in patients with allergic rhinitis.
- Effect of a single intranasal oxymetazoline on the PK of a single dose of intranasal ketorolac in patients with allergic rhinitis.
- Effect of a multiple doses of intranasal fluticasone propionate on the bioavailability of a single dose of intranasal ketorolac in patients with allergic rhinitis.

##### **Study Design:**

This was three-way study in 24 patients with allergic rhinitis as follows:

**Treatment A (Period 1):** Single intranasal dose of 30 mg ketorolac (15 mg in each nostril) on Day 1 (Period 1)

**Treatment B (Period 2):** Single standard intranasal dose of 0.05% solution of oxymetazoline (Drixin® = Afrin® in US) as 3 sprays in each nostril followed by 30 mg intranasal ketorolac (15 mg in each nostril) on Day 1 (Period 2). Ketorolac was administered 30 minutes after oxymetazolone administration.

**Treatment C (Period 2-3):** Seven days of treatment with a single standard dose of 200 mcg (2 x 50 mcg in each nostril) of fluticasone propionate (Beconase® = Flonase® in US) between Periods 2 and 3 followed by 30 mg intranasal ketorolac (15 mg in each nostril) on Day 1 (Period 3).

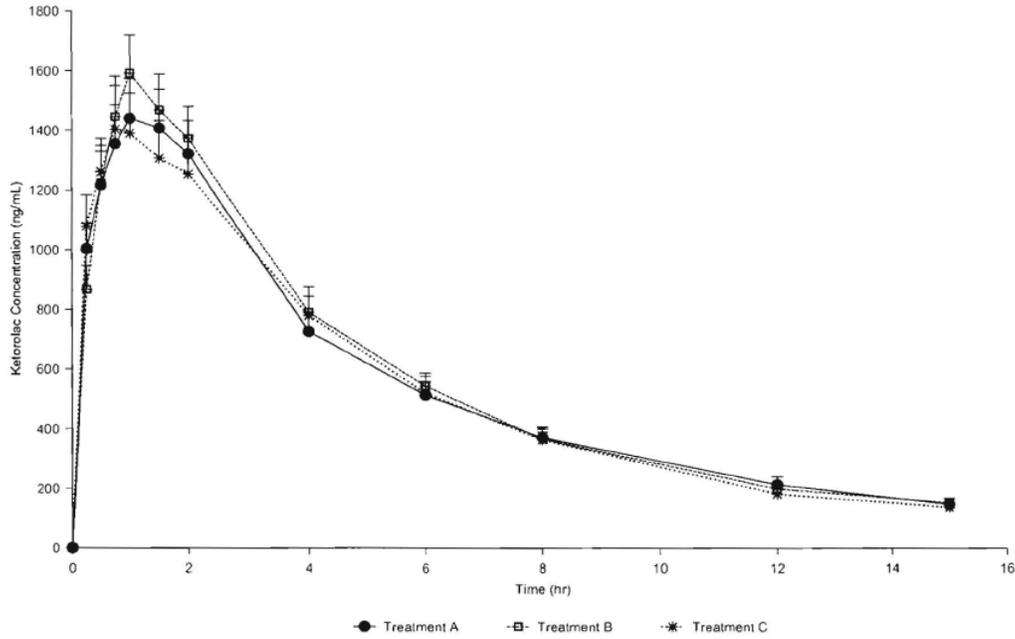
There was a washout of 2-7 days between periods.

The PK blood samples were collected over 24 hours post administration.

##### **Results:**

- Overall, the plasma concentration-time profiles following the three treatments were superimposable (**Figure 4.2.10.1**).
- The mean C<sub>max</sub> values (1630, 1729, and 1617 ng./ml and AUCs (9907, 9959, and 9445 ng.h/mL) virtually did not change following the three treatments (**Table 4.2.10.1**).
- However, in terms of 90% CI, both the C<sub>max</sub> and AUC were slightly outside the 80% to 125% regulatory/bioequivalence boundaries.

**Figure 4.2.10.1 Mean ( $\pm$  SE) Plasma Concentration-Time Profiles When Administered Alone or with Oxymetazoline or Fluticasone (Study # ROX-2007-03)**



**Table 4.2.10.1 Summary of Ketorolac PK Data When Administered Alone or with Oxymetazoline or Fluticasone (Study # ROX-2007-03)**

Parameter	Summary Statistic	Treatment		
		A	B	C
Number of subjects receiving treatment		24	24	24
$C_{max}$ (ng/mL)	n	24	24	24
	Mean	1630.223	1729.393	1617.810
	SD	653.599	684.055	766.328
$T_{max}$ (h)	n	24	24	24
	Median	1.000	1.250	0.875
	Range	0.25 – 2.00	0.75 – 2.05	0.25 – 4.00
$AUC_{0-t}$ (ng·h/mL)	n	24	24	24
	Mean	9001.8	9310.3	8794.3
	SD	4011.2	3200.2	4188.2
$AUC_{0-\infty}$ (ng·h/mL)	n	24	24	24
	Mean	9906.9	9959.1	9445.4
	SD	4347.0	3294.8	4308.2
$t_{1/2}$ (h)	n	24	24	24
	Mean	5.583	5.172	5.216
	SD	1.929	1.582	1.958
MRT (h)	n	24	24	24
	Mean	7.241	6.861	7.088
	SD	2.235	2.037	2.488

Data source: Section 14.3.3

Treatment A = Ketorolac Tromethamine i.n. given alone

Treatment B = Oxymetazoline Hydrochloride i.n. + Ketorolac Tromethamine i.n.

Treatment C = Fluticasone Propionate i.n. + Ketorolac Tromethamine i.n.

**Table 4.2.10.2 Statistical Analysis: Point Estimates and 90% of Ketorolac When Administered Alone or with Oxymetazoline or Fluticasone (Study # ROX-2007-03)**

Parameter	Test	Reference	n		Geometric LS Mean		Geometric LS Mean	90% CI for Geometric
			Test	Reference	Test	Reference	Ratio	LS Mean Ratio (%)
							(Test/Reference) (%)	[Lower – Upper]
C <sub>max</sub>	B	A	24	24	1581.24	1499.94	105.42	[87.13 - 127.54]
AUC <sub>0-t</sub>	B	A	24	24	8765.71	8063.26	108.71	[90.37 - 130.78]
AUC <sub>0-∞</sub>	B	A	24	24	9422.69	8929.37	105.52	[89.19 - 124.85]
C <sub>max</sub>	C	A	24	24	1419.50	1499.94	94.64	[78.22 - 114.50]
AUC <sub>0-t</sub>	C	A	24	24	7760.84	8063.26	96.25	[80.01 - 115.78]
AUC <sub>0-∞</sub>	C	A	24	24	8463.47	8929.37	94.78	[80.11 - 112.14]

Data source: Section 16.2.9.1

Treatment A = Ketorolac Tromethamine i.n. given alone

Treatment B = Oxymetazoline Hydrochloride i.n. + Ketorolac Tromethamine i.n.

Treatment C = Fluticasone Propionate i.n. + Ketorolac Tromethamine i.n.

### Conclusions:

Overall, the co-administration of oxymetazoline and fluticasone have no effect on the absorption and PK of intranasal ketorolac .

#### 4.2.11 Study # ROX-2002-02 (Scintigraphy)

**Objective:** The primary objective of this study is to determine the deposition of radiolabeled ketorolac in lungs and nasal cavity after intranasal administration in healthy subjects under three conditions:

- Gentle sniff-inhalation with subject standing
- Vigorous sniff-inhalation with subject standing
- Gentle sniff-inhalation with subject semi-supine.

#### Study Design:

This was three-way crossover study at single 30 mg ketorolac dose with a washout period of at least 44 hour between periods in 10 healthy subjects. Each subject received a single dose of <sup>99m</sup>Tc-DTPA labeled 30 mg ketorolac (15 mg as 100 µL solution in each nostril) as follows:

**Treatment A (Regimen A):** Gentle sniff-inhalation with subject upright for dosing and imaging

**Treatment B (Regimen B):** Vigorous sniff-inhalation with subject upright for dosing and imaging

**Treatment C (Regimen C):** Gentle sniff-inhalation with subject semi-supine for dosing and imaging

All regimens were administered using Valois nasal spray device which delivers 100 µl of solution as fine droplets, greater than 8 microns in diameter.

Scintigraphy images were performed at the following sites;

- Lateral nasal cavity and nasopharyna
- Posterior lung
- Posterior and anterior stomach if necessary
- Nasal wipes, if used
- Device

Retention in the nasal cavity and lungs were measured at 10, 20, 30, 45 minutes and at 2, 4, and 6 hours post-dose.

#### Results:

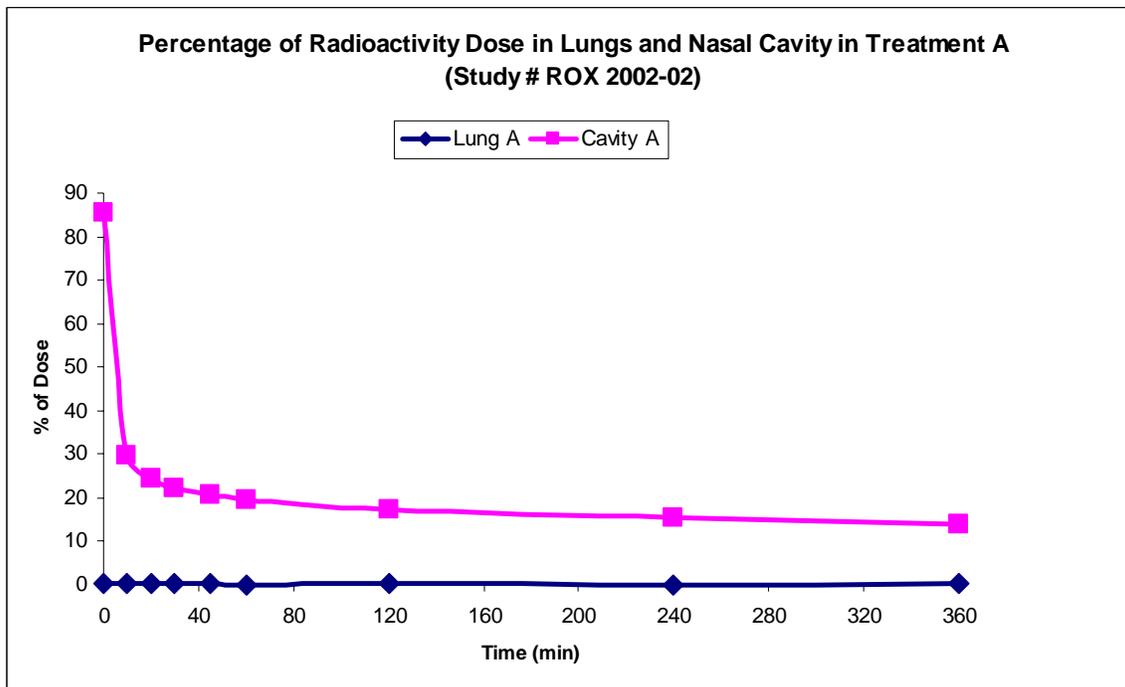
- In all treatments, the majority of radioactivity was found in nasal cavity immediately after dosing ranging from the mean of approximately 71% to 88% of the radioactivity dose (**Table 4.2.11.1**). The lowest activity was found in lungs at <0.5% of dose.
- There was a rapid decline in radioactivity over 6 hours in nasal cavity and lungs (**Figures 4.2.11.1-4.2.11.3 and Tables 4.2.11.2 and 4.2.11.2**).

**Table 4.2.11.1 Mean ( $\pm$  SD) Delivered % of Radioactivity Dose at Different Sites Immediately After Dosing (Study # ROX-2002-02)**

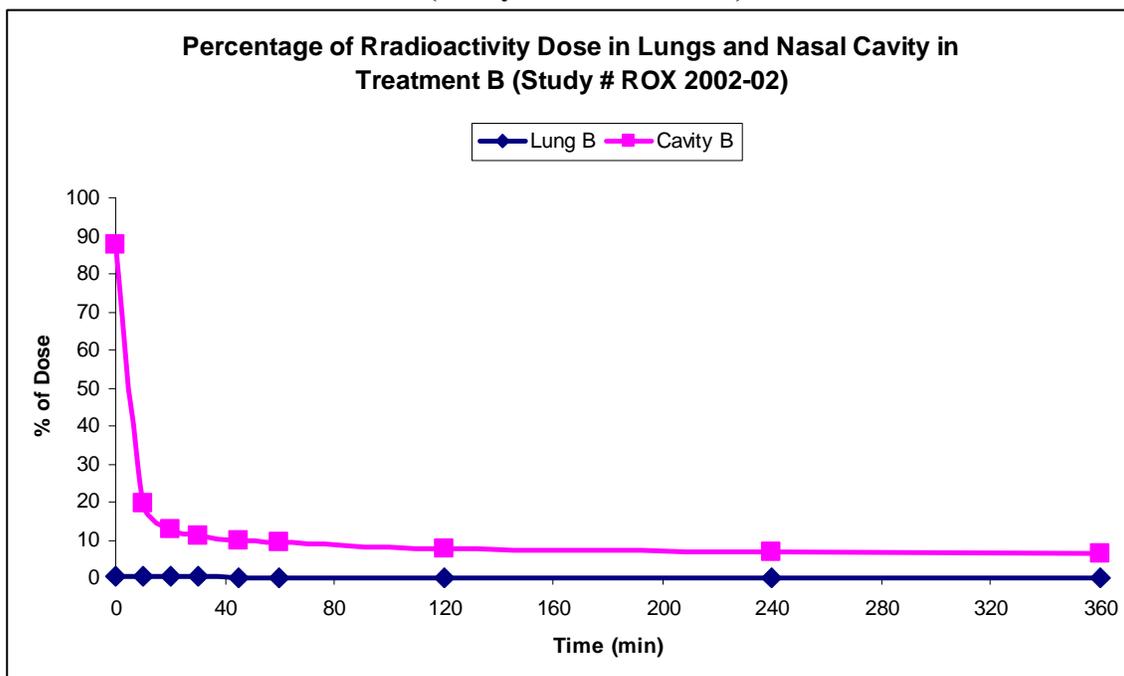
Regimen	Nasal cavity	Nasopharynx	Lungs	Oesophagus & stomach	Nasal Wipes
A	85.4 $\pm$ 15.4	0.6 $\pm$ 1.4	0.3 $\pm$ 0.2 <sup>a</sup>	4.3 $\pm$ 9.4	9.4 $\pm$ 11.9
B	87.8 $\pm$ 13.7	0.6 $\pm$ 1.7	0.4 $\pm$ 0.2 <sup>a</sup>	7.4 $\pm$ 9.3	2.8 $\pm$ 6.4
C	71.3 $\pm$ 22.7	2.1 $\pm$ 2.6	0.2 $\pm$ 0.2 <sup>a</sup>	19.2 $\pm$ 19.9	3.5 $\pm$ 6.6

<sup>a</sup> It is considered that these counts resulted from scattered radiation and that the true deposition of the ketorolac formulation in the lungs is zero or negligible.

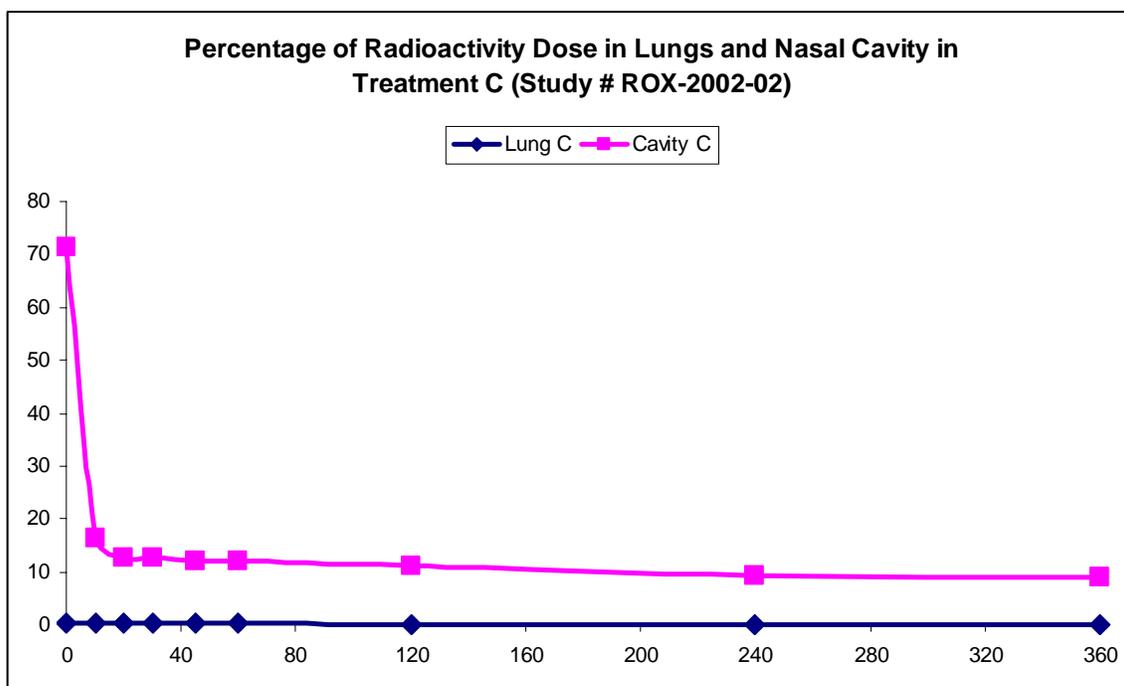
**Figure 4.2.11.1 Mean Delivered % of Dose in Lungs and Nasal Cavity in Treatment A (Study # ROX-2002-02)**



**Figure 4.2.11.2 Mean Delivered % of Dose in Lungs and Nasal Cavity in Treatment B (Study # ROX-2002-02)**



**Figure 4.2.11.3 Mean Delivered % of Dose in Lungs and Nasal Cavity in Treatment C (Study # ROX-2002-02)**



**Table 4.2.11.2 Mean ( $\pm$  SD) Delivered % of Radioactivity Dose over 6 hours in Lungs (Study # ROX-2002-02)**

Regimen	Time (minutes post-dose)								
	0	10	20	30	45	60	120	240	360
A	0.3 $\pm$ 0.2	0.3 $\pm$ 0.2	0.3 $\pm$ 0.2	0.2 $\pm$ 0.2	0.2 $\pm$ 0.2	0.1 $\pm$ 0.1	0.2 $\pm$ 0.2	0.1 $\pm$ 0.1	0.3 $\pm$ 0.3
B	0.4 $\pm$ 0.2	0.4 $\pm$ 0.4	0.4 $\pm$ 0.4	0.3 $\pm$ 0.3	0.2 $\pm$ 0.2	0.2 $\pm$ 0.2	0.2 $\pm$ 0.1	0.2 $\pm$ 0.2	0.2 $\pm$ 0.2
C	0.2 $\pm$ 0.2	0.3 $\pm$ 0.3	0.2 $\pm$ 0.2	0.3 $\pm$ 0.3	0.2 $\pm$ 0.2	0.2 $\pm$ 0.4	0.1 $\pm$ 0.2	0.1 $\pm$ 0.2	0.1 $\pm$ 0.2

**Table 4.2.11.3 Mean ( $\pm$  SD) Delivered % of Radioactivity Dose over 6 hours in Nasal cavity (Study # ROX-2002-02)**

Regimen	Time (minutes post-dose)								
	0	10	20	30	45	60	120	240	360
A	85.4 $\pm$ 15.4	29.8 $\pm$ 17.1	24.6 $\pm$ 13.5	22.1 $\pm$ 12.7	20.8 $\pm$ 11.8	19.5 $\pm$ 11.7	17.4 $\pm$ 11.1	15.3 $\pm$ 11.1	13.9 $\pm$ 10.2
B	87.8 $\pm$ 13.7	19.5 $\pm$ 17.1	12.6 $\pm$ 9.5	11.0 $\pm$ 7.7	10.0 $\pm$ 6.4	9.5 $\pm$ 5.9	7.6 $\pm$ 4.3	6.9 $\pm$ 4.2	6.5 $\pm$ 4.0
C	71.3 $\pm$ 22.7	16.4 $\pm$ 9.8	12.8 $\pm$ 6.7	12.7 $\pm$ 6.6	12.1 $\pm$ 5.8	11.9 $\pm$ 5.9	11.2 $\pm$ 6.0	9.4 $\pm$ 5.2	9.1 $\pm$ 5.6

**Conclusions:**

Overall, based on the data from this study virtually there was a negligible amount of radioactivity deposited in the lungs (<0.5%). The majority of the deposits were found in the nasal cavity (~70% to 85%).

### 4.3 Consult Review (Pharmacometric Review)

Not Applicable.

### 4.4 Filing Memo:

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	NDA 22-382	Brand Name	SPRIX®	
OCP Division (I, II, III, IV, V)	II	Generic Name	Ketorolac	
Medical Division	<b>DAARP</b>	Drug Class	Analgesic	
OCP Reviewer	Sayed (Sam) Al Habet, RPh., Ph.D.	Indication(s)	Moderate to Severe Pain	
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Solution	
Pharmacometrics Reviewer		Dosing Regimen	Q6-8h X 5 days	
Date of Submission	December 5, 2008	Route of Administration	Nasal	
Estimated Due Date of OCP Review	May/June 2009	Sponsor	Roxro Pharma	
Medical Division Due Date	July 2009	Priority Classification	Standard	
PDUFA Due Date	October 5, 2009			
<b>Clin. Pharm. and Biopharm. Information</b>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x	11		
<b>Healthy Volunteers-</b>				
single dose:	x	6		
multiple dose:	x	2		
<b>Patients-</b>				
single dose:		1		
multiple dose:		1		
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:		2		
fasting / non-fasting multiple dose:		2		
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:		3		

In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:		1		
geriatrics:		1		
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:		1		Across study analysis
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>		1		
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:		3		IM solution
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:		4		
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>		3		
<b>Total Number of Studies</b>		13		

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			x	Not electronic
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	deferred
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	deferred
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_yes\_\_\_ (see also attached filing slides, Attachment 1)**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Sayed (Sam) Al Habet, RP.h., Ph.D.  
2009

January 14,

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Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni, Ph.D.  
2009

January 14,

---

Team Leader/Supervisor

Date

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22382	----- ORIG 1	-----	----- KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/  
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SAYED AL HABET  
08/14/2009

SURESH DODDAPANENI  
08/14/2009

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

*General Information About the Submission*

	Information		Information
NDA/BLA Number	NDA 22-382	Brand Name	SPRIX®
OCP Division (I, II, III, IV, V)	II	Generic Name	Ketorolac
Medical Division	<b>DAARP</b>	Drug Class	Analgesic
OCP Reviewer	Sayed (Sam) Al Habet, RPh., Ph.D.	Indication(s)	Moderate to Severe Pain
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Solution
Pharmacometrics Reviewer		Dosing Regimen	Q6-8h X 5 days
Date of Submission	December 5, 2008	Route of Administration	Nasal
Estimated Due Date of OCP Review	May/June 2009	Sponsor	Roxro Pharma
Medical Division Due Date	July 2009	Priority Classification	Standard
PDUFA Due Date	October 5, 2009		

*Clin. Pharm. and Biopharm. Information*

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x	11		
<b>Healthy Volunteers-</b>				
single dose:	x	6		
multiple dose:	x	2		
<b>Patients-</b>				
single dose:		1		
multiple dose:		1		
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:		2		
fasting / non-fasting multiple dose:		2		
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:		3		
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

pediatrics:		1		
geriatrics:		1		
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:		1		Across study analysis
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>		1		
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:		3		IM solution
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:		4		
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>		3		
<b>Total Number of Studies</b>		13		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
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3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
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5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			x	Not electronic

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	deferred
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	deferred
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

### IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

\_\_\_yes\_\_\_ (see also attached filing slides, Attachment 1)

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.  
None

Sayed (Sam) Al Habet, RP.h., Ph.D.  
Reviewing Clinical Pharmacologist

January 14, 2009  
Date

Suresh Doddapaneni, Ph.D.  
Team Leader/Supervisor

January 14, 2009  
Date

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/s/

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Sayed Al-Habet  
1/27/2009 03:06:10 PM  
BIOPHARMACEUTICS

Suresh Doddapaneni  
1/27/2009 05:58:32 PM  
BIOPHARMACEUTICS