CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-450

PHARMACOLOGY REVIEW

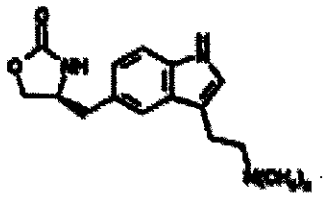
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA 21-450.
Review number:
Sequence number/date/type of submission: N-000 / stamp date 2-27-02 / New Drug Application, Original.
Information to sponsor: Yes () No (X).
Sponsor and/or agent: IPR Pharmaceuticals Inc., Carolina, Puerto Rico; Authorized US Agent: AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19803.
Manufacturer for drug substance: same as for already marketed oral products.

Reviewer name: Linda H. Fossom, Ph.D.
Division name: Neuropharmacological Drug Products.
HFD #: 120.
Review completion date: 12/18/02.

Drug:

Trade name: Zomig Nasal Spray.
Generic name (list alphabetically): zolmitriptan.
Code names: 311C90 (Wellcome); ZD8250 (AstraZeneca).
Chemical name: 2-Oxazolidinone, 4-((3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)methyl)-, (S)-.
CAS registry number: 139264-17-8.
Mole file number: unknown.
Molecular formula/molecular weight: C_{16}-H_{21}-N_3-O_2; 28'/—g/mol.
Structure:



Relevant INDs/NDAs/DMFs: NDA 20-768 (2.5 and 5 mg oral tablets for acute treatment of migraine attacks with or without aura; approved 11-25-97); NDA 21-231 (orally disintegrating tablets; approved 2-13-01); IND 45,147 (tablets); IND 53,8848 (nasal spray); IND 55,960 (fast-melt tablets).

Drug class: Agonist at serotonin receptor subtypes 5-HT1B/D.

Indication: Acute treatment of migraine with or without aura in adults.

Clinical formulation: aqueous solution, buffered to pH 5 using citrate phosphate buffer; preservative-free. Provided as a unit dose nasal spray, designed to deliver —— r 5 mg zolmitriptan in a dose volume of 100 µl, to the nasal cavity.

Route of administration: intranasal, as spray.

Disclaimer: Tabular and graphical information is excerpted directly from Sponsor's submission where ever feasible and noted as such.

Executive Summary

I. RECOMMENDATIONS

A. Recommendation on Approvability:

Approval.

B. Recommendation for Nonclinical Studies:

No additional pharmacology/toxicology studies are recommended.

C. Recommendations on Labeling:

[These labeling recommendations are compared with the Sponsor's proposed labeling and justified in the body of this review.]

CLINICAL PHARMACOLOGY/Mechanism of Action: Accept Sponsor's labeling, which is the same as the existing labeling for oral formulations.

Clinical Phamacokinetics and Bioavailability/Metabolism:

WARNINGS/Local Adverse Reactions:

PRECAUTIONS/Binding to Melanin-containing Tissues: Accept Sponsor's labeling including insertion of lack of effect on retina in intranasal animal studies; existing labeling for oral formulations includes this information for oral animal studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Carcinogenesis:

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Mutagenesis:

Mutagenesis: Zolmitriptan was mutagenic in an Ames test, in 2 of 5 strains of S. typhimurium tested, in the presence of, but not in the absence of, metabolic activation. It was not mutagenic in an *in vitro* mammalian gene cell mutation (CHO/HGPRT) assay. Zolmitriptan was clastogenic in an *in vitro* human lymphocyte assay both in the absence of and the presence of metabolic activation. Zolmitriptan was not clastogenic in *in vivo* mouse and rat micronucleus assays. Zolmitriptan was not genotoxic in an unscheduled DNA synthesis study.

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Impairment of Fertility: Accept Sponsor's labeling, which is the same as the existing labeling for the oral formulations.

Pregnancy: Pregnancy Category C: Recommended labeling (existing labeling for oral formulations) below:

Pregnancy: Pregnancy Category C: There are no adequate and well controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals was associated with embryolethality and fetal abnormalities. When pregnant rats were administered oral zolmitriptan during the period of organogenesis at doses of 100, 400, and 1,200 mg/kg/day, there was a dose-related increase in embryolethality which became statistically significant at the high dose. The maternal plasma exposures at these doses were approximately 280, 1,100, and 5,000 times the exposure in humans receiving the maximum recommended total daily dose of 10 mg. The high dose was maternally toxic, as evidenced by a decreased maternal body weight gain during gestation. In a similar study in rabbits, embryolethality was increased at the maternally toxic doses of 10 and 30 mg/kg/day (maternal plasma exposures equivalent to 11 and 42 times exposure in humans receiving the maximum recommended total daily dose of 10 mg), and increased incidences of fetal malformations (fused sternebrae, rib anomalies) and variations (major blood vessel variations, irregular ossification pattern of ribs) were observed at 30 mg/kg/day. Three mg/kg/day was a no effect dose (equivalent to human exposure at a dose of 10 mg). When female rats were given zolmitriptan during gestation, parturition, and lactation, an increased incidence of hydronephrosis was found in the offspring at the maternally toxic dose of 400 mg/kg/day (1,100 times human exposure).

II. SUMMARY OF NONCLINICAL FINDINGS

A. Brief Overview of Nonclinical Findings:

This NDA relies upon the preclinical studies that supported the approval of the oral formulations. Additionally, new preclinical studies were submitted that are adequate to support the change in route and qualification of 2 new impurities (——— and ——— whose specifications for the to-be-marketed nasal spray formulation are above threshold. These new studies did not indicate any new concerns for the nasal route of administration or attributable to the presence of the new degradants. (See "Overall Summary and Conclusions" in section IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS, at the end of this review.)

B. Pharmacologic Activity:

Zolmitriptan is a high affinity agonist at 5-HT1D serotonin receptors, but also has reasonably high affinity for the 5-HT1A receptor, which is thought to mediate CNS side effects, among others.

C. Nonclinical Safety Issues Relevant to Clinical Use:

There are no new preclinical concerns related to the nasal route of administration or attributable to the presence of the 2 new degradants (——— that required qualification.

III. ADMINISTRATIVE

A. Reviewer signature: Linda H. Fossom, Pharmacologist
{see appended electronic signature page}

B. Supervisor signature: Concurrence - Barry Rosloff, Team Leader
{see appended electronic signature page}

C. cc: list:
Chen, Lana
Oliva, Armando

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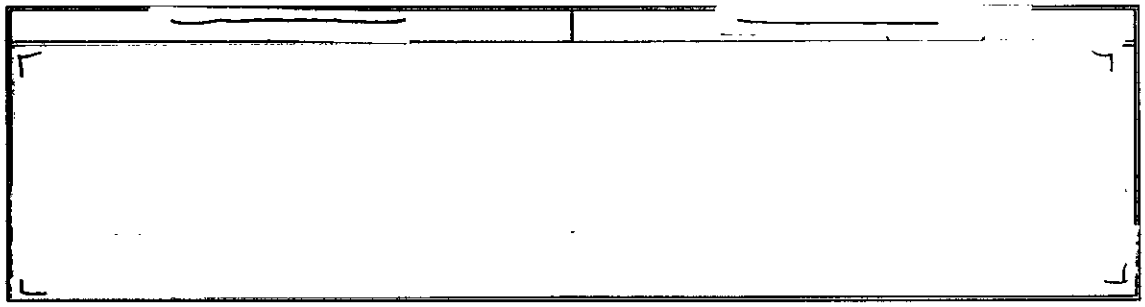
PHARMACOLOGY/TOXICOLOGY REVIEW

Introduction/Background: This NDA is for an intranasal route/formulation of zolmitriptan, a drug that is already approved as oral tablets (under NDA 20-768) and orally disintegrating tablets (under NDA 21-231). Normally, this NDA would only require preclinical testing in local toxicity studies and metabolism studies (if human studies indicated changes in systemic exposures or new metabolites), related to the change in route of administration.

However, the Sponsor has set specifications that require qualification for 2 degradants in the to-be-marketed Zomig Nasal Spray formulation. Although the maximum recommended single dose is 5 mg, the maximum recommended human daily dose is 10 mg. For maximum recommended human daily doses of 10 — mg, ICH Guidance (Q3B Impurities in New Drug Products, November 1996) recommends qualification of impurities present at ——— which ever is smaller; in this case. ——— ——is smaller and is the threshold for qualification. The specifications for impurities (degradation products) in the drug product are less than —, except for ——— ———, specification set at —, and ——— ———, specification set at ——(see structures, below). Qualification of these impurities requires: 1) a repeated-dose toxicology in one animal species of at least 2 weeks duration, 2) a minimal screen for genotoxicity, including *in vitro* tests for both mutations (Ames test) and chromosomal aberrations; and 3) because this drug will be used in women of child-bearing potential, our Division requests a Segment II reproductive toxicity study in one animal species.



In this NDA submission, the Sponsor has provided preclinical studies that satisfy the requirements for both the change in formulation and the qualification of the 2 degradants that exceed threshold. Local toxicity was determined with degraded formulation in 1-mo studies in rats and monkeys and in a 6-mo study in rats. Although several pharmacokinetic studies comparing exposures and metabolism by intranasal and oral routes in animals were provided, studies in humans did not indicate pharmacokinetic concerns; consequently, the animal studies were not reviewed in support of this submission. In terms of degradant qualification, the local toxicity studies using the degraded formulation satisfy the requirement for repeated-dose toxicity testing, because systemic exposures were adequate, maximum feasible doses were used, and general toxicity analysis was performed, including full histopathology. The Sponsor also submitted the required minimal screen of *in vitro* genotoxicity tests using the degraded

formulation, including the Ames test and a test for *in vitro* chromosomal aberrations (specifically, a human lymphocyte assay). [The Sponsor also submitted several *in vivo* chromosomal aberration studies using the degraded formulation; however, these would not have been required for qualification of degradants. These studies are discussed in Section V. Genetic Toxicology and in Appendix A.] Finally, the Sponsor submitted a Segment II reproductive toxicity test of degraded formulation administered orally to pregnant rats. These pivotal studies are reviewed in support of the application, below.

I. PHARMACOLOGY:

Pharmacology summary: The pharmacology studies for zolmitriptan were reviewed under NDA 20-768; no new pharmacology studies were submitted in the current NDA. Based upon the Review of NDA 20-768, zolmitriptan is a high affinity agonist at 5-HT1D serotonin receptors (pKi ~9), but also has "...reasonably high affinity for the 5-HT1A receptor (pKi 7.0), which is thought to mediate CNS side effects, among others."

Clinical Pharmacology/Mechanism of Action Labeling: No changes; same as labeling for Zomig® tablets and Zomig ZMT™ orally disintegrating tablets (see proposed labeling, excerpted below).

"

CLINICAL PHARMACOLOGY

Mechanism of Action

Zolmitriptan binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors. Zolmitriptan exhibits modest affinity for 5-HT_{1A} receptors, but has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, alpha$_1$-, alpha$_2$- or beta$_1$-adrenergic; H_1, H_2, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$ receptors. The N-desmethyl metabolite also has high affinity for 5-$HT_{1B/1D}$ and modest affinity for 5-HT_{1A} receptors.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (vasoactive intestinal peptide, substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of zolmitriptan for the treatment of migraine headache can most likely be attributed to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

"

Comments: Acceptable.

II. SAFETY PHARMACOLOGY:

Safety pharmacology summary: The safety pharmacology studies for zolmitriptan were reviewed under NDA 20-768; no new pharmacology studies were submitted in the current NDA. In brief, preclinical studies indicated that zolmitriptan had a potential for cardiovascular side effects. It increased blood pressure and heart rate in conscious dogs. It also resulted in a concentration-related contraction of human coronary artery *in vitro*; "this may be of some concern, as coronary vasospasm is one of the undesirable side effects of sumatriptan." The active human metabolite 183C91 was considered to be adequately examined for pharmacology and safety pharmacology.

III. PHARMACOKINETICS/TOXICOKINETICS:

Summary of human findings comparing intranasal to oral formulations/routes: The Sponsor submitted reports on 5 clinical pharmacology studies (conducted in Europe) that investigated pharmacokinetics of zolmitriptan nasal spray: Trials 0032, 0041, 0079, 0104, and 0102.

- Trial 0032: The results of this study, conducted by ——— the original developer of zolmitriptan, using a formulation with pH 7.4, are presented in the tables, below. From this data it is apparent that intranasal zolmitriptan does not achieve higher levels or AUCs for zolmitriptan or its major, active metabolite (183C91) than are produced by oral administration. [Subsequently, a formulation at pH 5.0 was used to improve stability at room temperature and avoid the need for keeping the formulation refrigerated.]

Sponsor's figures comparing plasma levels of zolmitriptan (upper panel) and its major, active metabolite (183C91; lower panel) following administration of 10 mg doses by oral and intranasal routes. [Trial 0032; excerpted directly from the electronic version of this submission, clinstat/clinpharmsum.pdf, pages 37 & 39.]

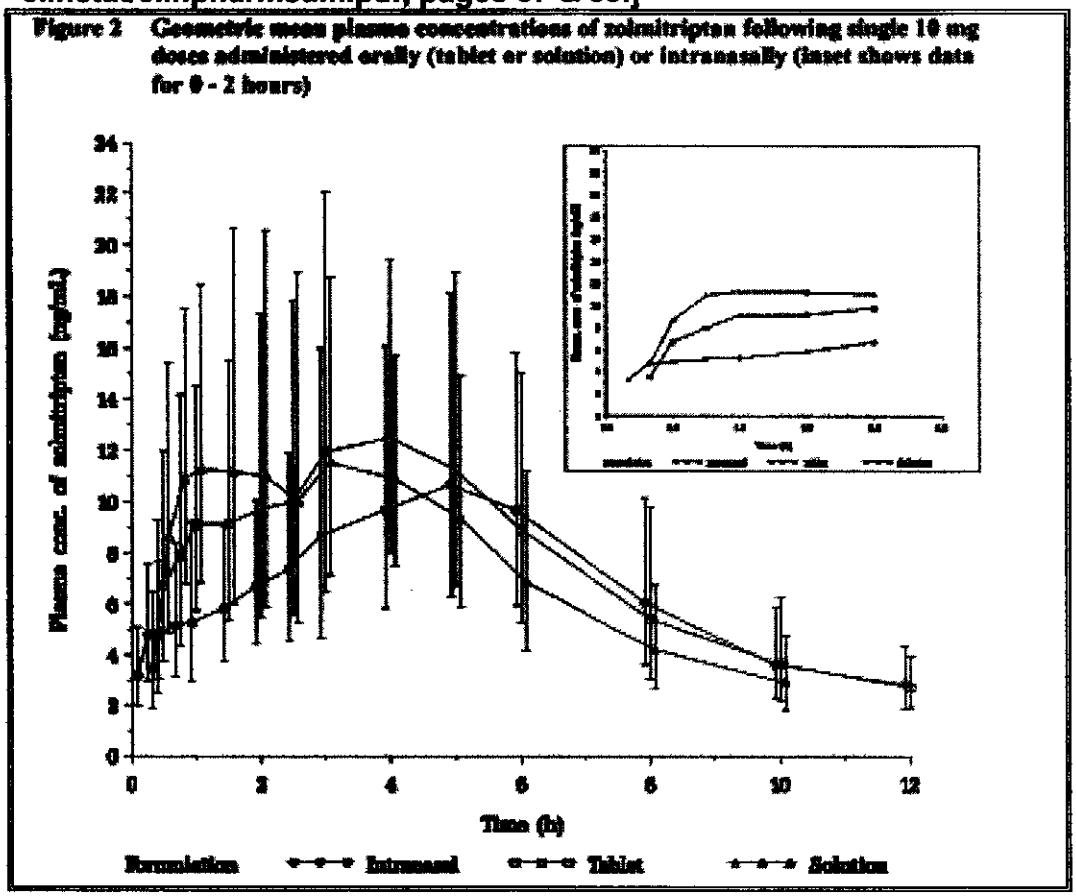
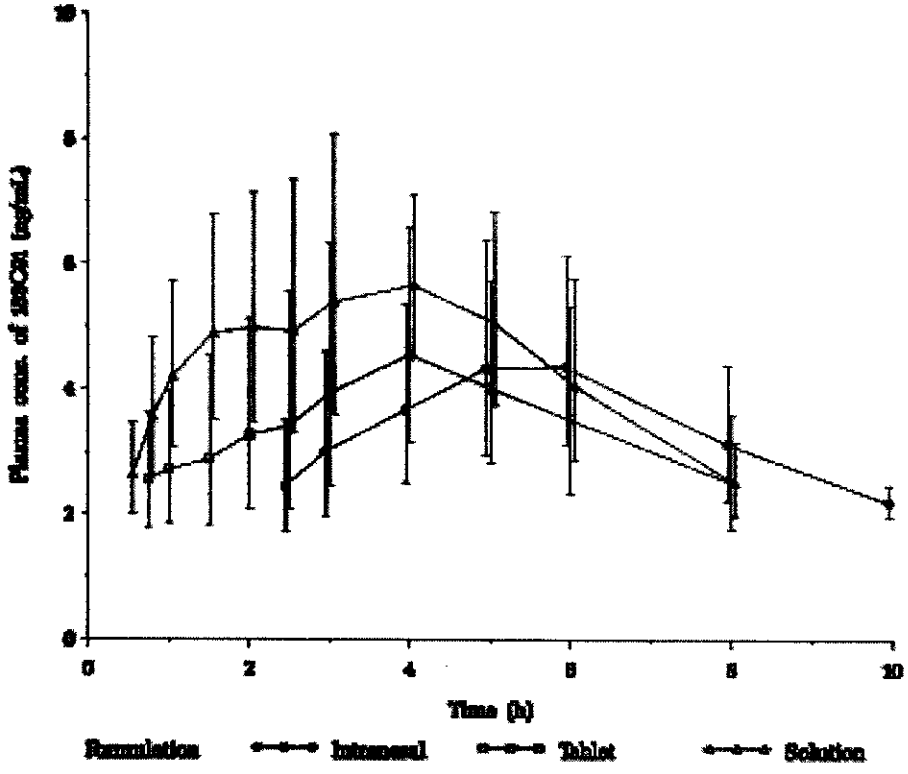


Figure 3 **Geometric mean plasma concentrations of 183C91 following single 10 mg doses of zolmitriptan nasal spray, tablet or oral solution**



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Sponsor's figures comparing PK parameters for zolmitriptan (upper panel) and its major, active metabolite (183C91; lower panel) following administration of 10 mg doses by oral and intranasal routes. [Trial 0032; excerpted directly from the electronic version of this submission, clinstat/clinpharmsum.pdf, pages 38 & 40.]

Table 6 Pharmacokinetic parameters for zolmitriptan and pharmacologically active metabolite 183C91 following single 10 mg doses administered intranasally or orally (tablet or oral solution)

Pharmacokinetic parameter	Treatment group Mean±SD[a]					
	n	Intranasal N=12	n	Oral tablet N=12	n	Oral solution N=12
Zolmitriptan						
C_{max} (ng/mL)	12	13.6±5.6	12	17.0±6.2	12	15.9±5.8
t_{max} (range) (h)[a]	12	4.00 (0.50 to 6.02)	12	3.00 (0.50 to 5.00)	12	2.00 (0.75 to 6.00)
AUC_{0-t} (ng·h/mL)	12	89.6±38.3	12	100.2±45.6	12	86.2±45.3
$AUC_{0-\infty}$ (ng·h/mL)	11	108.0±35.9	11	118.0±44.9	11	102.3±46.2
$t_{½}$ (h)	11	3.24±0.64	11	2.94±0.55	11	2.73±0.70
Vz/f (L)	11	509±256	11	398±191	11	418±131
CL/f (mL/min)	11	1812±752	11	1593±760	11	1907±831
MRT (h)	11	6.84±1.11	11	6.04±1.05	11	5.32±0.89
CL_R (mL/min)	11	226±65	11	218±66	11	239±164
Ae (% dose)	12	13.5±6.9	12	15.0±8.4	12	13.0±6.2
183C91						
C_{max} (ng/mL)	12	5.0±1.6	12	5.6±2.7	12	7.2±1.5
t_{max} (range) (h)[a]	12	5.00 (3.00 to 6.02)	12	4.00 (0.75 to 6.00)	12	3.00 (0.75 to 6.00)
AUC_{0-t} (ng·h/mL)	12	25.8±12.6	12	28.0±16.6	12	33.8±8.7
$t_{½}$ (h)	5	3.25±0.79	4	3.31±1.54	8	2.70±0.84
CL_R (mL/min)	5	152±42	4	139±15	8	163±51
Ae (% dose)	12	3.1±1.2	12	3.9±1.1	12	5.0±1.8

[a] Median calculated for t_{max}.

n Number evaluated.

C_{max}, maximum observed plasma concentration; t_{max}, time to maximum plasma concentration; AUC_{0-t}, area under the plasma concentration time curve from 0 to the last measured concentration at time t; $AUC_{0-\infty}$, area under the plasma concentration time curve from 0 to infinity; Ae, amount excreted in urine; CL/f, total body clearance; CL_R, renal clearance; MRT, mean residence time; $t_{½}$, terminal half-life; V_z/f, apparent volume of distribution.

Table 7 Pharmacokinetic parameters for 1652W92, and 2161W92 following single 10 mg doses of zolmitriptan nasal spray, tablet, or oral solution

Pharmacokinetic parameter	Treatment group Mean±SD[a]					
	n	Intranasal N=12	n	Oral tablet N=12	n	Oral solution N=12
1652W92						
C_{max} (ng/mL)	12	3.6±1.5	12	3.8±1.3	12	5.4±2.2
t_{max} (range) (h)[a]	11	5.00 (3.00 to 6.02)	11	4.00 (0.75 to 6.00)	12	2.50 (1.00 to 6.00)
AUC_{0-t} (ng·h/mL)	11	14.9±11.6	11	13.5±7.3	12	21.4±7.9
2161W92						
C_{max} (ng/mL)	12	9.1±4.6	12	11.8±4.6	12	15.8±4.5
t_{max} (range) (h)[a]	12	5.00 (3.00 to 8.00)	12	4.00 (1.50 to 6.00)	12	3.00 (1.50 to 6.00)
AUC_{0-t} (ng·h/mL)	12	58.6±34.6	12	61.7±19.1	12	85.4±25.5
$t_{½}$ (h)	8	3.76±1.03	9	3.67±1.03	11	2.84±0.76

[a] Median calculated for t_{max}.
n Number evaluated.
C_{max}, maximum observed plasma concentration; t_{max}, time to maximum plasma concentration; AUC_{0-t}, area under the plasma concentration time curve from 0 to the last measured concentration at time t; $t_{½}$, terminal half-life.

- Trial 0041 verified that absorption of zolmitriptan was not affected by the change in pH from 7.4 to 5.0.

- Trial 0079 determined that with 3 days of dosing and 2 doses separated by 2 hr each day there was no accumulation of zolmitriptan measured on day 4.

- Trial 0104 used PET methodology to assess the distribution of ^{11}C-labeled zolmitriptan (esp nasopharynx and upper abdomen and plasma) after intranasal administration.

- Trial 0102 determined that a sympathomimetic (vasoconstricting) nasal decongestant (xylometazoline —— w/v solution) administered intranasally 30 min before intranasal zolmitriptan (5 mg) did not alter PK parameters (AUC or Cmax) of zolmitriptan or 183C91.

PK/TK conclusions: The pharmacokinetic data from human studies comparing the intranasal and oral routes demonstrated that there was no increase in systemic exposures to zolmitriptan or its major metabolites; and no new metabolites were identified.

Consequently, although the Sponsor submitted several studies investigating the PK/TK of intranasal zolmitriptan in animals, these studies were not considered necessary to support the current NDA submission and have not been reviewed here; however, PK data was reviewed with toxicology studies, below, where relevant.

CLINICAL PHARMACOLOGY /Metabolism Labeling: Retained from labeling for Zomig tablets and Zomig ZM™ orally disintegrating tablets:

"

Metabolism: Zolmitriptan is converted to an active N-desmethyl metabolite such that the metabolite concentrations are about two-thirds that of zolmitriptan. Because the $5HT_{1B/1D}$ potency of the metabolite is 2 to 6 times that of the parent compound, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration.

"

The following was added to labeling for Zomig tablets and Zomig ZM™ orally disintegrating tablets:

"

[redacted]

"

Comments: [redacted]

PRECAUTIONS/Binding to Melanin-containing Tissues Labeling: Expanded from labeling for Zomig tablets and Zomig ZM™ orally disintegrating tablets:

"

Binding to Melanin-Containing Tissues: When pigmented rats were given a single oral dose of 10 mg/kg of radiolabeled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the value measured after 4 hours. This suggests that zolmitriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that zolmitriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with zolmitriptan were noted in any of the toxicity studies including those conducted by the nasal route [62,63,64,65]. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

"

Comments: This addition of information regarding the intranasal route is acceptable.

IV. GENERAL TOXICOLOGY:

Zolmitriptan has been approved under NDA 20-768 for clinical use as an oral tablet; general toxicology studies for oral zolmitriptan were reviewed under that NDA (John Jessop, Reviewer; review stamp-dated ~9/16/97).

For the new route of administration (intranasal) in the current application, additional general toxicology studies were/are required to determine local toxicity due to the intranasal route.

Additionally, the intranasal formulation contains 2 degradants whose specifications in the to-be-marketed product have been set above the threshold for qualification.

The Sponsor has submitted several repeated-dose toxicology studies in rats and monkeys:

311C90: 2 Week Oral (gavage) Toxicity Study in the Wistar Rat. Study E95376
Zolmitriptan: 28 Day Nasal Administration Toxicity Study in the Rat. Study TAR/2735
Zolmitriptan: 28 Day Nasal Administration Toxicity Study in the Rat. Study TAR/2813
Zolmitriptan: 26 Week Nasal Toxicity Study in Rat. Study TPR/2920
311C90: 4 Week Intranasal Toxicity Study in the Cynomolgus Monkey. Study E95373
Zolmitriptan: 28 Day Nasal Administration Toxicity Study in the Monkey. Study TAP/97
Zolmitriptan: Microscopic Evaluation Study of Root of Tongue in the Monkey. Study TKP/129

The following 2 studies are of particular interest for this application and are reviewed below:

- Study TPR/2920, a 6-mo intranasal study in rats using a degraded formulation of zolmitriptan and looking at general, as well as local, toxicity;
- Study TAP/97 (TKP/129 gives additional histopathology), a 28-day intranasal study in monkeys using a degraded formulation of zolmitriptan and looking at general, as well as local, toxicity [Study TAP/97 was reviewed in detail under IND 53,848, N-006].

The following studies are of lesser interest and are not reviewed in detail here:

- Study E95376 (in 1996, by ——— for ———— ———, is a 2-week oral study of degraded and non-degraded zolmitriptan solutions (batch no ———/5764, pH 5.0; ———, in rats; no description of degradation procedure nor certificates of analysis ("Data relating to the identity, purity and stability of the test or control materials are the responsibility of the Study Sponsor.");
- Study TAR/2735 (in 1997, by ———, for Zeneca Pharmaceuticals) is a 28-day nasal study of non-degraded zolmitriptan (powder, batch no Q12 42960) in rats. This study was reviewed in detail under IND 53,848, N-006; **doses of 18, 36, and 72**

mg/kg non-degraded zolmitriptan to Sprague-Dawley rats resulted in **dose- and time-related behavioral responses including paddling, squinting, and salivation; decreased weight gain and food consumption** in HDM; and **minimal to slight rhinitis** in MDM and HD males and females; and **minimal nasopharyngitis** in HD males and females;

- Study TAR/2813 (in 1998, by ———, for Zeneca Pharmaceuticals) is a 28-day nasal study of degraded and non-degraded zolmitriptan solutions {batch no PH/10828/26; C of A's estimated average amounts of ———, as ——— in rats. This study was reviewed in detail under IND 53,848, N-006; nominally **72 mg/kg non-degraded vs degraded** formulations to Wistar Hanover rats, resulted in duration-related **behavioral responses including paddling, squinting, and salivation**, that persisted throughout the 28–day treatment, as well as minimal to slight **rhinitis**;
- Study E95375 (in 1996, by ———, for ———, but Zeneca was on the distribution list for the report) is a 28-day nasal study of degraded (15 mg/kg) and non-degraded (batch no ——— '5764, pH 5.0; 30 mg/kg/day; 3 times daily bilateral impulsion of ~100ul into each nostril, with ~1 hr between administrations) zolmitriptan in monkeys; no description of degradation procedure ——— ——— nor certificates of analysis ("Data relating to the identity, purity and stability of the test or control materials are the responsibility of the Study Sponsor.").

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A. Study TPR/2920, a 6-mo intranasal study in rats using a degraded formulation of zolmitriptan and looking at general, as well as local, toxicity.

Study title: Zolmitriptan: 26 week nasal administration toxicity study in the rat.

Key study findings:

- No local or general toxicities in rats given maximally feasible intranasal doses up to HD of ~72 mg/kg/d for 6 mo;
- Systemic exposures were ~ half those achieved in the 2-yr rat (oral) carcinogenicity that supported the approval of the oral formulations.

Study no: ——— study no. 88/249; AstraZeneca reference no. TPR/2920.
Volume #, and page #: electronic submission 2/27/02: pharmtox\tox\dose\TPR2920.pdf; 668 pages.
Conducting laboratory and location: ——— ———
Date of study initiation: 1/19/99 (initial dose); until 9/15/99 (last necropsy); amended final report issued 8/00.
GLP compliance: yes, see page 11.
QA report: yes, see page 14.
Drug, lot #, and % purity —— test article ——— identified as Zomig Nasal Spray 50 mg/ml degraded (batch no. P/2569/18; in 10 ml vials); Certificate of Analysis (dated 12/9/98) noted pH as 5.0, assay as ——., with total degradants of ——, and ——— at —— and ——— at ——(by HPLC). The lot of drug substance was Q12, a blended sample of ——— ——— and ———

Formulation/vehicle: Control article (a clear colorless solution), identified as Placebo Zomig Nasal Spray (batch no. P/2569/17; in 12 ml vials); Certificate of Analysis (dated 12/9/98) noted pH as 5.0. The Sponsor indicated that the control article was —— w/v citric acid (anhydrous), —— sodium phosphate dodecahydrate, to pH5 in water for injection. [The Chemist, M. Heiman, informed me that this solution is hyper-osmotic; the to-be-marketed HD of 5 mg, 50 mg/ml is 420-470 mosmol/kg ———

Methods (unique aspects):
Dosing:

Species/strain: male and female Sprague-Dawley rats (HsdBrl:WH strain, ——

#/sex/group (main study): 20/sex at LD and MD and control-II; 30/sex at HD and control-I (but 10/sex in these groups were used for 8-week recovery phase). Satellite groups used for toxicokinetics or recovery: 6/sex at LD, MD, and HD for day 1 TK (discarded without necropsy); 9 main study rats/sex/dose were used for subsequent TK; 10 /sex in HD and control-I groups were used for 8-week recovery phase.

Age: ~ weeks at start of dosing.
Weight: males, 161-205 g, females, 129-158 g, at start of dosing.
Housing: in groups of 5 (main study) or 3 (satellites), in stainless steel mesh cages, food and water *ad libitum*, 12-hr light (0600-1800)/dark cycle,
Doses in administered units: nominally, 0, 6, 18, and 72 mg/kg/d (see Sponsor's table, below); HD "…considered to be the maximum practical level within the routine working day, based on the volume delivered and the use of [a degraded sample of] the clinical formulation of the test article." (see page 16.)

Sponsor's table showing number of instillations given to different dose groups. (Excerpted directly from this submission, electronic submission 2/27/02: pharmtox\tox\dose\TPR2920.pdf, page 20.]

Table 2 [redacted] **study number 88240. Sponsor reference number TPR/2920.**
Study design (1)

Group number	Group description	Instillations /animal/occasion	Sessions /day	Dose level ♦ (mg/kg/day)	Animals/group Main study + Male	Main study + Female	Satellites # Male	Satellites # Female
1	Control-I	2	6	0	30	30	-	-
2	Control-II	0.5♦	2➢	0	20	20	-	-
3	low	0.5♦	2➢	6	20	20	6	6
4	Intermediate	0.5♦	6	18	20	20	6	6
5	high	2	6	72	30	30	6	6

used for the toxicokinetic sampling on day 1 only. All satellite animals were killed and discarded without necropsy following this occasion. Nine main study animals/sex/group/sex with the lowest identification numbers were used for toxicokinetic blood sampling on subsequent occasions.

♦ Left and right nostrils given 1 instillation for alternate sessions

➢ The final two sessions of the day

◆ Based on 0.25 kg animal, and nominal volume of 15 µl.

+ 10 animals/group/sex with the highest identification numbers in the control-I and high dose group were maintained untreated for an 8 week treatment-free period.

Because a fixed dose (mg/d) was administered to each rat, the Sponsor calculated systemic doses (mg/kg) as the rats grew during the study (see table, below). Based upon the average mg/kg/day dose across the study and a conversion factor for nasal epithelium surface area compared with body weight (i.e., 10.4 cm^2/0.25 kg rat), the Sponsor calculated the average local dose, mg/ cm^2/day (see table, below). The HD produced average local doses of 1.3 and 2.0 mg/ cm^2/day in males and females, respectively.

Sponsor's table showing actual doses of zolmitriptan administered to rats, based upon increasing body weights. [Excerpted directly from this submission, electronic submission, 2/27/02: pharmtox\tox\dose\TPR2920.pdf, page 21.]

Table 3 [redacted] **study number 98/249. Sponsor reference number TPR/2920. Study design (2)**

Group Number	Group description	Overall mean dose level - males (mg/kg/day) §	Overall mean dose level - females (mg/kg/day) §	Actual dose level for week (mg/kg/day) § Male 1	Male 4	Male 13	Male 26	Female 1	Female 4	Female 13	Female 26
1	Control-I	0	0	0	0	0	0	0	0	0	0
2	Control-II	0	0	0	0	0	0	0	0	0	0
3	low	4.3 (0.10)	6.8 (0.16)	6.8	5.3	4.0	3.5	9.1	7.7	6.6	6.1
4	intermediate	12.3 (0.30)	20.7 (0.50)	20.2	15.4	11.5	9.9	28.0	23.6	20.1	18.2
5	high	52.3 (1.26)	83.7 (2.01)	83.2	65.1	49.8	42.0	114.1	96.1	80.7	73.2

§ based on weekly body weights

( ) dose level (mg/cm²/day) expressed in terms of nasal epithelium surface area of 10.4 cm² for a 0.25kg rat (Schneider, 1983)

Route, form, volume: nasal instillation, up to 2/session and up to 6 sessions per day, depending upon dose (see Sponsor's table, above).

Observations and times:

Clinical signs: daily, for overt toxicity or ill health; immediately and 5 min post-dosing, daily for first week, then 1 day per week to end of study; detailed physical exam weekly.

Body weights: before treatment on first day of study; then at weekly intervals; before necropsy.

Food consumption: weekly, per cage; calculated as g/rat/week. (Water consumption was measured daily in weeks 15 and 16, to investigate possible dehydration as explanation for anomalous results in several clinical chemistry parameters in week 13.)

Ophthalmoscopy: all main study rats pre-treatment; controls (I and II) and HD at weeks 13 and 25.

EKG: not performed.

Hematology and Clinical Chemistry: blood (3 x 0.5 ml; from caudal vein after overnight fast) from main study rats, 10/sex/group, in weeks 13 and 26; repeated in week 15 because of anomalous results in week 13.

Urinalysis: overnight, without food and water, from 10/sex/group main study rats (not the same ones that were used for hematology and clinical chemistry), in weeks 12 and 25.

Gross pathology, Organs weighed, and Histopathology: See histopathology table. Nasal cavity and pharynx were examined on all main study rats; other histopathology was on controls and HD, only. [NB included is a statement signed by a DR. [redacted] confirming "...that the histopathological examination of tissues in this study included assessment of nasal

and respiratory passages in representative tissue sections, and that the examination was adequate to assess toxicity to all tissues of the respiratory system." Signed 6/16/02; see page 13.]

The nasal turbinates were examined at 4 levels (excerpted directly from this submission, page 28; page 13 of study report):

Level A (anterior turbinate) taken between posterior side of incisor incisors and 2 to 4 mm in front of anterior edge of first palatine fold;
Level B (anterior) immediately behind Level A to approximately 1 mm behind the edge of the first palatine fold
Level C (posterior turbinate) between first and second palatine fold
Level D (posterior) between posterior edge of second palatine fold and anterior edge of third palatine fold.

Toxicokinetics: blood (0.4 ml; caudal vein) from satellite rats on day 1 and from 9/sex/dosed group of main study rats in week 26; at 0 (or immediately before dosing), and 30 min, 2, 4, 8, and 1 hr after dosing.

Results:

Mortality: 1 HDF (#215) died in week 23; cause of death: (slight) hemorrhage in the thoracic cavity (especially in tissue adjacent to aorta bifurcation noted in histopathology; approximately 2 ml red fluid in thoracic cavity noted on gross exam) of unknown causes, considered not to be related to specific toxicity of zolmitriptan.

Clinical signs: At weekly physical exams, there was increased incidence of fur staining at HD; and from week 7 onward, increased incidence of protruding eyes in females in HD and HD vehicle control-I group.

Post-dosing in drug-treated rats only, paddling, salivation and sniffing were noted immediately after dosing, but subsided within minutes of being returned to home cages. All 3 signs/behaviors were observed in several HD rats on day 1, and essentially all HD rats after 1 week through the end of the study.

Body weights: slightly (~10%) decreased body weight gain for HD males only during weeks 1-4.

Food consumption: slightly decreased during weeks 1-4 in HD males; dosed females tended to eat more than controls throughout the study.

Water consumption: Although water consumption tended to be increased (~6%) in dosed rats compared with control-II rats during the 2 weeks that were measured (weeks 15, 16), the differences are not compelling (values are per cage, not for individual rats).

Ophthalmoscopy: Sponsor states that there were no treatment-related abnormalities during weeks 13 or 25 at HD, compared with control-I; other groups were not tested. [No data was presented.]

Electrocardiography: not performed.

Hematology: No remarkable findings in week 13 or week 26.

Clinical chemistry: No remarkable findings. However, several (3) MDFs (#200, #195, and #199) had high levels of urea (2.5-, 3.6-, and 6.3-fold mean control, respectively) and creatinine (2.3-, 3.0-, and 5.9-fold mean control, respectively) at week 13. Clinical chemistry was repeated at week 15 to investigate these findings, but values were normal at that time. The Sponsor noted that blood samples were generally more difficult to obtain in weeks 13 and 15 than would have been expected. Water consumption was measured in weeks 15 and 16 (see above), however, only cage averages were obtained, not amounts for individual rats. Complete histopathology was only done on controls and HD rats, so it cannot be determined whether these 3 MDF rats had sequelae in their kidneys.

Urinalysis: Urine volume was decreased in LDF (↓~35%) and HDF (↓~42%), with slightly (non-significantly) increased specific gravity, compared with controls, at week 12; urine volume was non-significantly decreased in MDF (27%), with no alteration in specific gravity. Results were similar at week 26.

Organ weights: There were no treatment-related changes in organ weights after 26 weeks of dosing. The absolute testes+epididymides weights were slightly (~15%) decreased in HD males, compared with control-I males, after the 8-week recovery phase, however, this effect was not statistically significant when weights were normalized to body weights.

Gross pathology: There were no findings suggestive of treatment-related local or systemic toxicity. The only unusual finding was in 3/10 HD males at recovery: small and soft testis.

Histopathology: There were no findings indicative of treatment-related local or systemic toxicity. Specifically there were no findings in the nasal cavity or respiratory tract of the HD rats, compared with control rats (see table, below).

Potentially cancerous or pre-cancerous findings (in the tissues in the table, above) were generally rare and not correlated with drug treatment (see table, below). Although lymphoid hyperplasia in the mandibular lymph node was relatively common, it was not more common in (HD) drug-treated rats than in controls. Additionally, 2 HD females showed slight bronchiolo-alveolar hyperplasia (and 1 minimal) and this was not noted in any control rats. However, this hyperplasia occurs spontaneously in rats (*Histopathology of Preclinical Toxicity Studies*, by P. Greaves, Elsevier, 2000) and the incidence and severity were very low in the current study. It should also be noted that there were no lung carcinogenicity findings in the oral 2-year rat study (NDA 20-768) at considerably higher doses (oral doses up to 400 mg/kg) and systemic exposures to zolmitriptan (AUCs of 300-400 μg.hr/ml at 400 mg/kg, compared with ~30 μg.hr/ml at the HD in the current study).

Table showing histopathology findings related to local toxicity. Number codes for groups are 1 and 2 for control groups, 3 for LD (~6 mg/kg), 4 for MD (~18 mg/kg), and 5 for HD (~72 mg/kg). [Compiled/excerpted from Sponsor's summary table.]

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=T;FIND=ALL;SUBSET=ALL	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	20	20	20	20	20	20	20	20	20	19
[redacted]	NUMBER EXAMINED:	20	20	20	20	19	20	20	20	20	19
--OLFACTORY ATROPHY		0	0	0	0	1	2	0	0	0	0
--[redacted]		0	0	0	0	0	0	0	0	0	2
--EOSINOPHILIC GLOBULES		1	0	0	0	0	4	0	0	0	0
--INFLAMMATORY CELL FOCI		5	0	0	2	0	1	0	0	3	2
--[redacted]		3	0	0	1	0	1	0	0	0	2
--[redacted]		1	0	0	0	0	0	0	0	0	0
[redacted]	NUMBER EXAMINED:	20	20	20	20	19	20	20	20	20	19
--[redacted] HYPERPLASIA		0	0	0	1	0	0	0	0	0	0
[redacted]	NUMBER EXAMINED:	20	20	0	0	20	20	20	0	0	19
--[redacted]		1	0	0	0	0	0	0	0	0	0
--[redacted]		1	5	0	0	1	3	0	0	0	0
[redacted]	NUMBER EXAMINED:	20	20	0	0	20	20	20	0	0	19
--[redacted]		2	6	0	0	0	1	0	0	0	0
--[redacted]		0	0	0	0	0	1	0	0	0	0
[redacted]	NUMBER EXAMINED:	20	20	1	2	20	20	20	1	0	19
--FOAMY HISTIOCYTES		8	11	0	1	12	11	10	1	0	11
--ALVEOLAR PIGMENT/HEMOSIDIN		0	0	0	0	1	0	0	0	0	0
[redacted]	NUMBER EXAMINED:	20	20	1	2	20	20	20	1	0	19
--ALVEOL CONGESTION/HEMORRHAGE		0	2	1	2	1	0	0	0	0	0
--INFLAMMATORY CELL FOCI		11	4	0	1	5	3	7	1	0	7
--[redacted]		0	1	0	0	2	2	0	0	0	0
--CHOLESTEROL GRANULOMA		0	1	0	0	0	1	1	0	0	0
--[redacted]		0	1	0	0	0	1	0	0	0	2
--[redacted] HEMANGIOMA		1	2	0	0	1	0	0	0	0	0
--[redacted]		0	0	0	0	0	0	0	0	0	2
[redacted]	NUMBER EXAMINED:	17	20	0	0	20	20	20	0	0	18
--LYMPHANGIECTASIS		0	0	0	0	0	0	0	0	0	1
--LYMPHOID HYPERPLASIA		0	0	0	0	0	1	0	0	0	0
[redacted]	NUMBER EXAMINED:	20	20	2	3	20	20	20	4	4	19
--ACINAL CONGESTION/HEMORRHAGE		3	2	1	3	2	3	5	4	4	5
--LYMPHANGIECTASIS		0	0	0	1	0	1	1	0	0	2
--LYMPHOID HYPERPLASIA		5	7	2	1	8	6	5	1	2	7
LACRIMAL GLAND	NUMBER EXAMINED:	20	20	0	0	20	20	20	0	0	19
--LOBULAR ATROPHY		0	0	0	0	0	2	0	0	0	0
--INFLAMMATORY CELL FOCI		3	2	0	0	3	2	0	0	0	3
--ADENITIS		1	0	0	0	1	0	0	0	0	0
--HARDERIAN GLAND ALTERATION		2	5	0	0	3	1	0	0	0	1
EYE	NUMBER EXAMINED:	20	20	0	0	20	20	20	3	2	19
--RETINAL ATROPHY		5	2	0	0	2	7	2	2	1	5
--RETINAL FOLD		0	2	0	0	0	0	0	0	0	0

With regard to systemic toxicity, the incidence of hemopoiesis in the spleen was higher in HD rats than controls (16/20 HDM and 17/19 HDF, compared with 7/20 control males and 10/20 control females); however, this finding was not noted at much higher systemic doses (oral doses up to 400 mg/kg/d) in the 6-mo study reviewed for NDA 20-768. Additionally, the 3 HD males with grossly abnormal testis at recovery (#112, 114, and 115) also showed tubular atrophy; however, 3/20 control-II rats also had tubular atrophy

after 26 weeks of dosing and there was no mention of testes pathology in the 6-mo study reviewed for NDS 20-768.

Toxicokinetics: Systemic exposures (AUCs) to zolmitriptan were ~ 30 µg.hr/ml at the HD of ~72 mg/kg after 26 weeks of dosing (see table, below). This is approximately half the systemic exposure achieved after 26 weeks of oral dosing at 100 mg/kg in the 2-year carcinogenicity study (see review of NDA 20-768).

Zolmitriptan:

Table 1 Study number 88/249. Summary of toxicokinetic parameters

Parameter	0 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	271.5	1151.4	1164.7	1456.2	4980.4	13668.0
C_{max} (ng/mL)	35.4	175.7	246.0	257.7	657.8	2183.3
t_{max} (h)	0	2	2	0.5	4	4

Table 2 Study number 88/249. Summary of toxicokinetic parameters

Parameter	6 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	503.8	502.5	941.5	2090.2	3856.6	3675.5
C_{max} (ng/mL)	45.5	90.5	124.7	249.2	382.5	665.1
t_{max} (h)	2	2	0.5	0	0	0

183C91:

Table 3 Study number 88/249. Summary of toxicokinetic parameters

Parameter	6 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	NC	NC	NC	NC	NC	NC
C_{max} (ng/mL)	NC	NC	NC	NC	21.9	37.5
t_{max} (h)	NC	NC	NC	NC	4	2

NC not calculated

Table 4 Study number 88/249. Summary of toxicokinetic parameters

Parameter	6 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	NC	NC	NC	NC	NC	NC
C_{max} (ng/mL)	NC	NC	NC	49.7	23.4	NC
t_{max} (h)	NC	NC	NC	8	0.5	NC

NC not calculated

1652W92:

Table 5 Study number 88/249. Summary of toxicokinetic parameters

Parameter	Day 1					
	6 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	NC	NC	NC	NC	799.9	616.2
C_{max} (ng/mL)	NC	NC	47.4	NC	112.1	109.6
t_{max} (h)	NC	NC	2	NC	0.5	2

NC not calculated

Table 6 Study number 88/249. Summary of toxicokinetic parameters

Parameter	Week 26					
	6 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	NC	NC	NC	NC	783.2	208.4
C_{max} (ng/mL)	NC	NC	29.8	80.1	88.1	50.1
t_{max} (h)	NC	NC	0.5	8	0	0

NC not calculated

2161W92:

Table 7 Study number 88/249. Summary of toxicokinetic parameters

Parameter	Day 1					
	6 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	NC	NC	NC	NC	329.5	646.4
C_{max} (ng/mL)	NC	NC	NC	NC	41.3	91.2
t_{max} (h)	NC	NC	NC	NC	4	2

NC not calculated

Table 8 Study number 88/249. Summary of toxicokinetic parameters

Parameter	Week 26					
	6 mg/kg/day		18 mg/kg/day		72 mg/kg/day	
	Males	Females	Males	Females	Males	Females
AUC_{0-24h} (ng.h/mL)	NC	NC	NC	NC	321.1	454.7
C_{max} (ng/mL)	NC	17.9	NC	109.3	37.7	93.4
t_{max} (h)	NC	2	NC	6	0.5	0

NC not calculated

B. Study TAP/97 (TKP/129 gives additional histopathology of the root of the tongue), a 28-day intranasal study in monkeys using a degraded formulation of zolmitriptan and looking at general, as well as local, toxicity.

Study title: Zolmitriptan: 28 day nasal administration toxicity study in the monkey (— study no. 88/203; Sponsor [Zeneca Pharmaceuticals] ref no. TAP/97); and Zolmitriptan: Microscopic evaluation study of root of tongue in the monkey (— study no. 88/328; Sponsor [AstraZeneca UK Limited] ref no. TKP/129).

This 28-day toxicology study (TAP/97) has been previously reviewed in detail under IND 5(,848 (N-006, review stamp-dated 9/16/99). I will rely upon that review for general toxicity (e.g., clinical chemistry, etc), but will re-review the local toxicity data, including the histopathology for the root of the tongue submitted as study TKP/129.

Key study findings:

- No evidence of local or general toxicity at maximally feasible intranasal doses up to ~64 mg/kg/d.

Study no: — study no. 88/203; Sponsor [Zeneca Pharmaceuticals] ref no. TAP/97; and (— study no. 88/328; Sponsor [AstraZeneca UK Limited] ref no. TKP/129.
Volume #, and page #: electronic submission 2/27/02: pharmtox\tox\dose\TAP97.pdf (235 pages) and \TKP/129.pdf (53 pages).

Conducting laboratory and location: —

Date of study initiation: 1/21/98 (first dose); through 3/19/98 (last necropsy).
GLP compliance: yes, see page 9.
QA report: yes, see page 12.
Drug, lot #, radiolabel, and % purity: test article (—), identified as "Zomig Nasal Spray (50 mg/ml)" (batch no. P/10828/52); Certificate of Analysis (dated 1/15/98, with results from 5 samples) demonstrated average pH of 5.2, assay of (— mg/ml, with total degradants of — and —, at (— and — at — (by HPLC). The lot of drug substance was Q12, a blended sample of (— (— and (— states that analysis of contents of the unused bottles at the end of the study verified the stability of the degraded formulation, since the concentration of zolmitriptan was —, and of — was — (the amount of — was not reported).
Formulation/vehicle: Control article (a clear colorless solution), identified as Placebo Zomig Nasal Spray (batch no. PH/10828/56; in 12 ml vials); Certificate of Analysis (dated 1/15/98) noted pH as 5.2. The Sponsor indicated that the control article was — w/v citric acid (anhydrous), — sodium phosphate dodecahydrate, to pH5 in water for injection. [The Chemist, M. Heiman, informed me that this solution is hyper-osmotic; the

to-be-marketed HD of 5 mg, 50 mg/ml is 420-470 mosmol/kg

Methods (unique aspects):

Dosing:

Species/strain: male and female purpose-bred cynomolgus monkeys (*Macaca fascicularis*) from

#/sex/group (main study): 3/sex/dose, with additional 3/sex at control and HD for recovery phase.

Satellite groups used for recovery: 3/sex at control and HD.

Age: young adults.

Weight:

Housing: individually, in stainless steel cages; 12-hr light (0700-1900)/dark cycle; each monkey was offered 100g food each day after 1st dosing, with a 25 g biscuit and piece of fruit after 5th dosing; water *ad libitum*.

Doses in administered units: nominally, 0, 16, 32, and 64 mg/kg/d (see table, below). The Sponsor calculated local doses, mg/ cm^2/day, based upon the average mg/kg/day dose calculated across the study and a conversion factor for nasal epithelium surface area compared with body weight (i.e., 61.6 cm^2/7 kg Rhesus monkey) (see table, below). The HD produced an average local dose of 7.5 mg/ cm^2/day.

Sponsor's table showing number of instillations given to different dose groups. (Excerpted directly from this submission, page 18; page 5 of study report.]

Table 2 — Study number [illegible]. Sponsor reference number TAP/97.

Study Design

Group number	Group description	Instillations/ nostril /session	Sessions /day	Nominal dose level+ (mg/kg/day)	Actual dose level+ (mg/kg/day)	Animals/group Male	Female
1	control	2	8	0	0	6*	6*
2	low	0.5#	8	16 (1.82)	16.6 (1.89)	3	3
3	intermediate	1	8	32 (3.64)	33.1 (3.76)	3	3
4	high	2	8	64 (7.27)	66.2 (7.52)	6*	6*

left and right nostrils given 1 instillation for alternate sessions

+ based on 2.5 kg animal, and nominal volume of 100µL

* actual dose levels based on overall actual mean body weight (2.08kg), overall daily mean delivery of 93µL and actual concentration of test article of —

() dose level(mg/cm²/day) expressed in terms of nasal epithelium surface area of 61.6cm² for a 7kg Rhesus monkey, and assuming a linear relationship between body weight and surface area, i.e. 22cm² for a 2.5kg monkey (Schreider, 1983)

* 3 animals/sex were maintained for a 4-week treatment-free period

Route, form, volume, and infusion rate: both test and control articles were supplied as multi-shot nasal devices that delivered nominally 100ul per instillation (verified with 3 dosers by — but data not presented). Each monkey

received 8 sessions per day with 0.5 to 2 instillations per nostril per session (see table, above). Sessions were spaced ~45 min apart.

Observations and times:

Clinical signs: daily for signs of ill health or overt toxicity; detailed physical exams at weekly intervals.
Body weights: weekly and before necropsy.
Food consumption: calculated as g/monkey/week.
Ophthalmoscopy: on all monkeys pre-treatment and after a final dosing session in week 4; by indirect ophthalmoscopy, under ketamine, with mydriatic agent.
EKG: on all monkeys pre-treatment and ~ 1 hr after a final dosing session in week 4.
Hematology & Clinical chemistry: blood samples (3 x 1 ml, from femoral vein/artery) before treatment and on day 22, after overnight fast.
Urinalysis: urine collected overnight from all monkeys pre-treatment and in week 4; water-deprived 2-3 hr before and during collection.
Gross pathology, Organs weighed, & Histopathology: See histopathology table. [NB included is a statement signed by the study pathologist ([redacted] confirming "...that the histopathological examination of tissues in this study included assessment of nasal and respiratory passages in representative tissue sections, and that the examination was adequate to assess toxicity to all tissues of the respiratory system." Signed 10/20/98; see page 11.] Nasal cavity from all monkeys, in addition to ~10% of monkeys, were peer reviewed by the Sponsor.

The nasal cavities were examined at 4 levels (excerpted directly from this submission, page 23; page 10 of study report TAP97.pdf):

a 4 levels where: Level 1 - sample of nasal vestibule complete with septum but without conchae; Level 2 - sampled at the level where the superior conchae form small projections and the inferior conchae form large projections into the nasal passage; Level 3 - sampled at the level where the middle conchae are attached to the roof the nasal passage. Present are small projections of superior and inferior conchae; Level 4 - sampled at the level of the orbits. Usually the maxillary sinuses are present with some evidence of superior and inferior conchae.

Toxicokinetics: blood samples (~0.5 ml, from femoral vein/artery) from all dosed monkeys at 0, ½, 2, 4, 8, and 18 hr after the final dosing session on days 1 and 28; plasma levels of zolmitriptan and 3 major metabolites (183C91, 165W92, and 2161W92) were determined by LC-MS.

Results:

Mortality: no deaths.

Clinical signs: none in control monkeys; occasional salivation, vomiting; red discharge from the nose of 1 HDF on day 1 and 1 MDF on day 3.

Body weights: No notable effects.

Food consumption: transient decrease in food consumption in some dosed monkeys, that resolved in week 2 or 3.

Ophthalmoscopy: The Sponsor states, "There were no abnormalities detected in the eyes of any animal;" however, no data were presented.

Electrocardiography: The Sponsor states that "in week 4, there were no clear patterns of variation of waveforms on the traces, or variations in the heart rate which could be related to treatment." No "waveform" data presented, but individual heart rates before or after dosing in week 4 were no different from those before treatment was initiated.

Hematology, Clinical chemistry & Urinalysis: No remarkable findings.

Organ weights: Decreased weights of spleens (MD and HD males, not evident at recovery) and pituitaries (HD males, absolute and relative, still evident at recovery), but without hispathology.

Gross pathology: No remarkable findings.

Histopathology: No remarkable findings. Specifically, there were no treatment-related findings in nasal cavity or lung (see table, below) and no findings for the lymph nodes or eyes or for the root of the tongue (study TKP129).

Table showing histopathology findings related to local toxicity. Number codes for groups are 1 for control group, 2 for LD (~16 mg/kg), 3 for MD (~32 mg/kg), and 4 for HD (~64 mg/kg). [Compiled/excerpted from Sponsor's summary table.]

[redacted]								
[redacted]								
[redacted]								
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
[redacted]	3	3	3	3	3	3	3	3
[redacted]	3	3	3	3	3	3	3	3
--[redacted]	2	2	0	0	0	0	0	1
--[redacted]	1	1	0	0	0	0	1	1
[redacted]	3	3	3	3	3	3	3	3
--[redacted]	1	0	0	0	0	0	0	1
--[redacted]	0	0	0	0	1	0	0	0
--[redacted]	1	2	3	3	2	2	1	0
--[redacted]	3	3	1	3	2	3	1	3
--[redacted]	0	0	0	1	0	0	0	0
--[redacted]	1	2	0	1	0	1	1	1

Toxicokinetics: Zolmitriptan displayed proportional kinetics at these dosages; there was no evidence of accumulation or sex-rated differences. In terms of metabolism, only 2161W92 was present in plasma at significant levels (exposures of ~25% of zolmitriptan, based upon either $AUC_{0\text{-}18hr}$ or C_{max}). In plasma: [zolmitriptan] > [2161W92] >> [1652W92] ≅ [183C91], which were essentially undetectable. Systemic exposures to zolmitriptan after 28 days of dosing were: AUCs of approximately 440, 570, and 1200 ng-hr/ml and Cmax's of approximately 47, 56, and 175 mg/ml at 16, 32, and 64 mg/kg/day, respectively.

General toxicology summary: Local and general toxicity was determined for degraded formulation of zolmitriptan in 1-mo studies in rats and monkeys and in a 6-mo study in rats. The Sponsor estimated local doses of zolmitriptan based upon values for surface areas of nasal cavity in different species from a book chapter authored by J. P. Schreider (In: *Nasal Tumors in Animals and Man*, vol III, *Experimental Nasal Carcinogenesis*, CRC Press, Boca Raton, FL, 1983). I calculated the local dose for humans from the maximum recommended daily human dose of 10 mg, correcting the 181 cm^2 surface area listed in that reference for a 70 kg human to 160 cm^2 for a 60 kg human; the local human dose for 10 mg/60 kg/day is 0.062 mg/cm^2.

There was no local or general toxicity in monkeys given maximally feasible intranasal doses up to ~64 mg/kg/d for 1 month. This dose is 380-times or 71-times the maximum recommended human daily dose of 10 mg on a mg/kg or mg/m^2 basis, respectively. The estimated local dose is 120-times the estimated local human dose (of 0.062 mg/m^2).

Non-degraded zolmitriptan administered intranasally at doses up to 72 mg/kg/d to rats for 1 month resulted in dose- and time-related behavioral responses, including paddling, squinting, and salivation. Decreased weight gain and food consumption was seen in HD males. Additionally, there was some indication of local irritation, with minimal to slight rhinitis in MD males (36 mg/kg/d) and HD males and females; and minimal nasopharyngitis in HD males and females. These findings were at least partly replicated using intranasal administration of non-degraded and degraded formulations in a 1-month rat study. The behavioral responses and minimal to slight rhinitis were seen in rats given both degraded and non-degraded zolmitriptan; however, no suppression of body weight gain was apparent.

In contrast, there was no local toxicity in rats given maximally feasible intranasal doses of degraded zolmitriptan formulation up to HD of ~72 mg/kg/d for 6 months. Specifically there was no increased incidence of rhinitis as had been seen in the 1-month studies. Additionally, there were no cancerous or precancerous lesions related to the intranasal route, in the nasal cavity, respiratory tract, eyes, or associated lymph nodes. General toxicity was limited to behavioral responses similar to those seen 1-month studies. Systemic exposures were ~ half those achieved in the 2-yr rat (oral) carcinogenicity that supported the approval of the oral formulations. The HD of 72 mg/kg is 420-times or 68-times the maximum recommended human daily dose of 10 mg on a mg/kg or mg/m^2 basis, respectively. The estimated local dose is 21-times or 32-times the estimated local human dose (of 0.062 mg/m^2) for male and female rats, respectively.

It should be noted that the safety margins for the 2 degradants being qualified (———————) are at least as great as those for zolmitriptan, because the percentage of each degradant in the degraded formulations used in the pivotal preclinical

studies was always greater than the specification for that degradant in the to-be-marketed formulation.

General toxicology conclusions: The 1-mo studies in rats and monkeys and the 6-mo study in rats where degraded zolmitriptan was administered intranasally support both the change in route of administration (from oral to intranasal) and the qualification of the 2 degradants —— and —— . There is no new general or local toxicity associated with the change in route or presence of the degradants.

Histopathology Inventory for NDA #21-450.

Study	6-mo	28-day
Species	rat	monkey
Adrenals	X*	X*
Aorta	X	x
Bone Marrow smear	X	X
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix	X	
Colon	X	X
Duodenum	X	X
Epididymis	X*	X
Esophagus	X	X
Eye	X	X
Fallopian tube		
Gall bladder	n/a	X
Gross lesions	X	X
Harderian gland	X	
Heart	X*	X*
Ileum	X	X
Injection site		
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland	X	x
Larynx	X	X
Liver	X*	X*
Lungs	X*	X*
Lymph nodes, bronchial	X	X
Lymph nodes, cervical		X
Lymph nodes mandibular	X	X
Lymph nodes, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity	X	X
Optic nerves	X	X
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X	X
Peripheral nerve		x
Pharynx	X	
Pituitary	X*	X*
Prostate	X*	X*

Rectum	X	x
Salivary gland	X	X
Sciatic nerve	X	x
Seminal vesicles	X	x
Skeletal muscle	X	x
Skin	X	X
Spinal cord	X	X
Spleen	X*	X*
Sternum	X	X
Stomach	X	X
Testes	X*	X*
Thymus	X	X
Thyroid	X*	X*
Tongue	X	X[+]
Trachea	X	X
Urinary bladder	X	X
Uterus	X	X*
Vagina	X	x
Zymbal gland	X	
Standard List		

X, histopathology performed
*, organ weight obtained
[+], histopathology on monkey tongue was done under study TKP129.
NB: in 6-mo rat study nasal cavity and pharynx were examined on all main study rats; other histopathology was on controls and HD, only.

V. GENETIC TOXICOLOGY:

NDA 20-768 for (non-degraded) zolmitriptan has been approved and labeling reflects mutagenicity in the Ames test (in 2/5 of the S. typhimurium tested, in presence of metabolic activation only) and *in vitro* clastogenicity in HLA, with and without metabolic activation. However, (non-degraded) zolmitriptan was not clastogenic *in vivo* in a mouse micronucleus assay. Additionally, it was not genotoxic *in vitro* in a mammalian cell (CHO/HGPRT) mutation assay or in an unscheduled DNA synthesis assay.

A. Bacterial mutagenicity (Ames test)

The approved (non-degraded) zolmitriptan was tested in TA1535, TA1537, TA1538, TA98, TA100, and was strongly positive in strains TA1538 and TA98, at 3,000 and/or 10,000 µg/plate with metabolic activation only (but neither positive repeated in second studies). TA102 or E. coli strains were not tested, as has been recommended since 1994. Although the positives did not replicate, the Reviewer (J. Jessop) felt (and I agree) that they indicated mutagenic potential for zolmitriptan and this was conveyed in the labeling.

For the current submission, an initial Ames test study with degraded drug (TMV752) was performed using strains TA1535, 1537, 98 and 100 and 2 E. coli strains. Although this study included one of the strains that was positive in the initial study for NDA 20-768 (i.e., TA 98), the other positive strain (i.e., TA1538) was not included. (Certificate of Analysis indicated [redacted] This study was not reviewed in detail for this submission, however, it should be noted that there was no indication of positive findings in this study.

In a 2nd study (TMV/902), degraded nasal spray formulation was again tested in the same strains as the 1st study, because of a variation in the degradant specification (Certificate of Analysis indicated [redacted] [NB The current (to-be-marketed) specifications are [redacted] for [redacted] and [redacted] for [redacted]. This study is reviewed in detail, below.

Study title: Degraded zolmitriptan nasal spray formulation: Bacterial mutation assay in *S. typhimurium* and *E. coli*.

Key findings:

- **Valid and negative** for degraded Zomig nasal spray formulation containing 2 degradant that require qualification at amounts greater than the specifications for to-be-marketed product (i.e., [redacted] at [redacted] and [redacted] at [redacted].
- **The positive finding for mutagenicity (for non-degraded zolmitriptan) in the Ames test should remain in labeling for the nasal spray.**

Study no: YV4596 (Sponsor ref no. TMV/902).

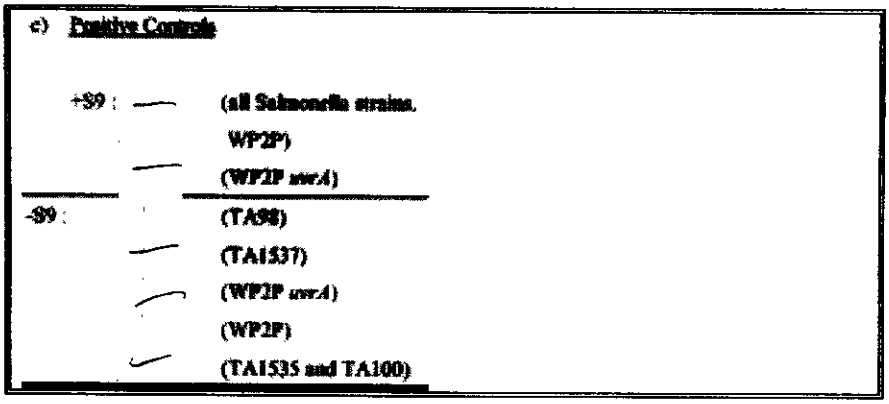
Study type: bacterial mutation (Ames) test.
Volume #, and page #: electronic submission 2/27/02: pharmtox\tox\muta\TMV902.pdf (37 pages).
Conducting laboratory and location: [redacted], Sponsor: AstraZeneca UK Limited.
Date of study initiation: 1/24/00.
GLP compliance: yes, see page 6.
QA reports: yes, see page 8.
Drug, lot #, and % purity: [redacted] test article [redacted], identified as "Zomig Nasal Spray 50 mg/ml degraded" (batch no. P/2569/18); Certificate of Analysis (dated 12/9/98) noted pH as 5.0, assay as [redacted], with total degradants of [redacted] and [redacted] at [redacted] and [redacted], at [redacted] (by HPLC). The lot of drug substance was Q12, a blended sample of [redacted] and [redacted].

Formulation/vehicle: The degraded zolmitriptan nasal spray served as a stock solution, with dilutions in DMSO.

Methods:

Strains: *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 (detect A-T mutations); *E.coli* strains WP2P [WP2 (pKM101)] and WP2P *uvrA* [WP2 *uvrA* (pKM101)] (detect G-C mutations and cross-linking).
Dose selection criteria:
Basis of dose selection:
Range finding studies:
Test agent stability: in view of short duration of study, no additional stability testing was done.
Metabolic activation system: S9 fraction from livers of male Sprague-Dawley rats induced with phenobarbital/β-naphthoflavone (once daily for 3 dasy); S-9 mix contained 10% S-9 fraction, v/v.
Controls:
Vehicle: DMSO.
Negative controls: DMSO (100 µl)
Positive controls: see table, below (excerpted directly from this submission, pages 11 and 13).

Chemical	Supplier	CTL Ref	Solvent
[redacted]		Y03243/003	DMSO
		Y01142/006	DMSO
		Y00111/005	DMSO
		Y01165/002	DMSO
		Y02125/001	DMSO
		Y02201/001	H_2O
		Y06019/001	H_2O



Exposure conditions:

Incubation time: 3 days at 37 degrees.

Doses used in definitive study: 0, 100, 200, 500, 1000, 2500, and 5000 µg/plate; used for all strains in all experiments.

Study design: 1st experiment: standard plate-incorporation protocol, with and without S9, with concurrent controls. 2nd experiment: 60-min pre-incubation protocol, with and without S9, with concurrent controls; 3rd experiment, standard plate-incorporation, TA1535 strain without S9, only, with concurrent controls;

Analysis:

No. of replicates: within each experiment, n=3 for zolmitriptan, n=2 for positive controls without S9, n=3 for positive controls with S9, n=5 for negative controls.

Counting method: automatic colony counter "adjusted appropriately to permit the optimal counting of mutant colonies.

Criteria for positive results: See quote from report, below. It should be noted that statistical analyses were done using a one-tailed Student's t-test and "the corresponding probability for each dose level was derived by computer using the appropriate degrees of freedom."

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A positive response in a (valid) individual experiment is achieved when one or both of the following criteria are met:

a) a statistically significant dose-related increase in the mean number of revertant colonies is obtained;

b) a two-fold or greater increase in the mean number of revertant colonies (over that observed for the concurrent solvent control plates) which is statistically significant, is observed at one or more concentrations.

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Summary of individual study findings:

Study validity: valid: adequate strains of bacteria, 6 amounts of drug (~2-fold spacing) with highest amount 5000 µg/plate; triplicate plates; strong positive

controls. NB The report did not address whether there was any cytotoxicity. However, I assume there was not cytotoxicity at the amounts used in these experiments (i.e., ≤5000 µg/plate), because from the review of NDA 20-768, cytotoxicity was not apparent at 3160 µg/plate, but was at 10,000 µg/plate.

Study outcome: negative, for all strains tested, in replicate experiments, with and without metabolic activation.

The Sponsor did not provide a concise summary table, however, there was only a sngle instance of a possibly positive effect. For strain TA1535 in the 2nd study, the mean number of colonies at only 2 doses without activation, 200 and 2500 µg/plate, were just over twice the negative control value (means of 16.8 (13, 14, 15, 20, 22) for controls, 38.0 (28, 37, 49) at 200 µg and 40.0 (20, 44, 56) at 2500 µg. In the 1st study, there was no indication of a positive for this strain, with mean values of 12.2, 17.3, 8.0, 10.7, 14.3, 8.3, and 13.3 for 0, 100, 200, 500, 1000, 2500, and 5000 µg/plate, respectively. Additionally, when this strain was retested in experiment 3, there was also no indication of a positive, with mean values of 10.0, 11.3, 11.3, 11.3, 10.3, 12.7, and 8.3 for 0, 100, 200, 500, 1000, 2500, and 5000 µg/plate, respectively.

NB No mutagenicity was found for degraded zolmitriptan in the study submitted under the current NDA. Additionally, one of the strains that produced a strong (though unreplicated) positive finding with non-degraded zolmitriptan with metabolic activation in the study submitted under NDA 20-768, that is TA98, was not positive in the current study. However, the other strain that produced such a strong (though unreplicated) positive finding with metabolic activation in the study submitted under NDA 20-768, that is TA1538, was not tested in the current NDA. **The positive finding for mutagenicity (for non-degraded zolmitriptan) in the Ames test should remain in labeling for the nasal spray.**

B. *In vitro* clastogenicity

It should be noted that (non-degraded) zolmitriptan was found to be clastogenic in the human lymphocyte assay, both in the absence and presence of metabolic activation (see review of NDA 20-768; and labeling).

Study title: Zolmitriptan: Degraded nasal spray formulation: *In vitro* cytogenetic study using cultured human lymphocytes. [A comparison of degraded to non-degraded formulations.]

Key findings:

Study no: TYX124.
Study type: *in vitro* clastogenicity.
Volume #, and page #: electronic submission 2/27/02: pharmtox\tox\muta\TYX124.pdf (80 pages).
Conducting laboratory and location: AstraZeneca UK Limited, Alderley Park, Macclesfield, Cheshire, England; [redacted] did slide analysis.
Date of study initiation: 7/16/01 (start of culture treatment).
GLP compliance: yes, see pages 2 and 11.
QA reports: yes, see pages 3 and 14.

Drug, lot #, radiolabel, and % purity: zolmitriptan as nasal spray formulation: 1) **degraded formulation**: Zomig Nasal Spray (50mg/ml), batch ref no. P/1631/26C [redacted] degraded and packaged in 10 ml vials], end of test analysis (10/18/01) indicated pH 5.1, zolmitriptan at 45 mg/ml, with total degradants at [redacted] (by HPLC), including [redacted] at [redacted] and [redacted] at [redacted] 2) **non-degraded formulation:** Zomig Nasal Spray (50mg/ml), batch ref no. P/1631/36 [packaged in 10 ml vials], end of test analysis (10/18/01) indicated pH 5.0, zolmitriptan at [redacted] with total degradants at [redacted] (by HPLC), including [redacted] at [redacted] and [redacted] at [redacted]

Formulation/vehicle: non-degraded and degraded Zomig Nasal Spray formulations (see above).

Methods:

Strains/species/cell line: human lymphocytes, from blood of healthy donors.
Dose selection criteria:

Basis of dose selection: initial cytotoxicity testing.
Range finding studies: cytotoxicity testing at nominal concentrations of 0, 5, 10, 39.5, 100, 500, and 1000 µg/ml of degraded and non-degraded formulations, with and without metabolic activation, for 3 and without activation for 20 hr. High concentration was limited by concentration of zolmitriptan (and degradants) in stock solution (keeping the amount of added

drug solution to no more than — of the incubation volume, i.e., 200ul/10ml culture medium). There was no clear, dose-related decrease in MI; however, there was a tendency for all drug-treated cultures without S9 to be lower than controls.

Test agent stability: test articles were assayed before and after use, with no significant change in amounts of zolmitriptan or degradants ' — or —.

Metabolic activation system: rat liver S9 fraction (not further described).

Controls:

Vehicle: Zomig Nasal Spray Placebo: 0.93% citric acid, to pH 5 with disodium hydrogen phosphate dodecahydrate.

Negative controls: vehicle.

Positive controls: mitomycin C (without activation); cyclophosphamide.(with activation).

Comments: adequate.

Exposure conditions:

Incubation and sampling times: drug treatment for 3 with and without activation and 20 hr without activation; all cells were harvested 20 hr after initiation of treatment.

Doses used in definitive study: 0, 100, 250, 400, 700, 85, and 1000ug/ml in absence of S9; 0, 750, 850, and 1000ug/ml in presence of S9.

Study design: 1st: cytotoxicity test (based upon decreased mitotic index; number of cells in metaphase/100 cells scored); 2nd: cytogenetics assay (chromosomal aberrations).

Analysis:

No. of replicates: for chromosomal aberrations: duplicate cultures for each drug treatment; quadruplicate cultures for solvent controls.

Counting method: manual; 100 cells/culture (only 25 for positive controls); 1 duplicate was analyzed by AstraZeneca, the other by ' —

Criteria for positive results: The Sponsor compared non-degraded to degraded formulaitons with regard to the incidence of aberrant cells (including and excluding gaps).

Summary of individual study findings:

Study validity: valid.

Study outcome: The degraded formulation (containing more of degradants — —, and ' — than the specification limit) appeared to be no more clastogenic than the non-degraded formulation in this assay. Furthermore, the labeling for the marketed tablet formulation of zolmitriptan (i.e., non-degraded) states that it "... was clastogenic in an *in vitro* human lymphocyte assay both in the absence of and the presence of metabolic activation."

C. *In vivo* clastogencity

It should be noted that (non-degraded) zolmitriptan was not clastogenic *in vivo* in a mouse micronucleus assay (see review of NDA 20-768; and labeling).

For the change from oral to nasal route of administration, even with the need to qualify degradants in the nasal formulation, an additional *in vivo* clastogenicity assay would not be required. Nonetheless, the Sponsor submitted several micronucleus assays; these studies are not reviewed in detail in support of the current submission, however, the results are summarized below.

In an initial micronucleus assay for degraded zolmitriptan in male rats (study TQR2894) that appeared to be (arguably) positive 48 hr after a single oral dose of 1000 mg/kg (nominally). At that dose and time, an average of —— were counted in —— /rat (7 rats/group), compared with 0 in the control (the 24 hr controls had —— per ——).

The Sponsor performed a 2nd rat micronucleus assay (study TQR3080) comparing degraded and non-degraded formulations in males and females, counting MPEs in —— PEs rat). In this study, there was no indication of increased MPEs in male rats treated with oral doses up to 1000 mg/kg (non-degraded or degraded); however, in females there were statistically significant trends for both non-degraded and degraded zolmitriptan at 48 hr only. It should be noted that the control value for females at 48 hr was very low, —— in ——PEs, compared with ——for 24-hr female controls, ——for 24-hr male controls, and ——for 48-hr male controls. Furthermore, the historical control provided with this study showed very low values, with no MPEs found in —— PEs from approximately half the rats.

The Sponsor performed a 3rd rat micronucleus assay (study TQR/3142) comparing degraded and non-degraded zolmitriptan in males and females, but counting —— PEs per rat (3-times more than in previous studies). In this study, control values were more reliable, with ——MPE counted for essentially all control rats (6/7 males at 24 hr and females at 48 hr; 7/7 males at 48 hr and females at 24 hr). The average control group values ranged from ——. There was no evidence on zolmitriptan-related increases in number of MPEs —— PEs, with either degraded or non-degraded formulations.

The Reviewer considers this last study of micronucleus formation in rats, with a more reliably measurable control level, as definitive and negative.

At about the same time that the Sponsor was conducting the last (and definitive) rat micronucleus assay, they contracted with —— to perform a micronucleus assay in male and female mice using degraded zolmitriptan (study TQM/126). Oral doses up to 1000 mg/kg did not increase the mean incidence of MPEs/—— PEs in male mice at 24 or 48 hr or female mice at 24 hr. The incidence of MPEs was increased in female mice at 48 hr by trend test, however, only the high dose of 1000 mg/kg was more than twice controls

[redacted] MPEs/ [redacted] PEs). Additionally, it should be noted that (deja vu) the control value for females at 48 hr [redacted] was approximately half that for males or females at 24 hr or for males at 28 hr (group mean values ranged from 1.0-1.2). When the study was repeated for females only and 48 hr only, the control value was higher ([redacted] PEs) and there was no effect of zolmitriptan treatment (déjà vu all over again). The Reviewer considers this also a negative study.

Consequently, these micronucleus assays in rats and mice are considered negative and do not require modification of the current labeling that says zolmitriptan was negative in a mouse micronucleus assay.

D. Additional genotoxicity studies

None submitted.

E. Genetic toxicology summary: Degraded zolmitriptan formulations were tested for *in vitro* mutagenicity (Ames test) and *in vitro* clastogenicity (human lymphocyte assay). The degraded formulation was negative in a valid Ames test. The *in vitro* clastogenicity was similar for degraded and undegraded formulations in the human lymphocyte assay. Additionally, the degraded formulation was negative in a mouse micronucleus assay; this had been found to be true for non-degraded zolmitriptan in a mouse micronucleus assay submitted under NDA 20-768 for the oral formulation. Finally, degraded and non-degraded zolmitriptan were determined to be negative in a definitive rat micronucleus assay.

F. Genetic toxicology conclusions: The studies submitted with this NDA support the qualification of degradants [redacted] and [redacted]

G. Labeling recommendations: **Changed from labeling for Zomig tablets and Zomig ZM™ orally disintegrating tablets:**

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ON ORIGINAL

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

VI. CARCINOGENICITY:

Carcinogenicity conclusions: Zolmitriptan has been approved under NDA 20-768 for clinical use as an oral tablet; carcinogenicity studies for zolmitriptan in rats and mice were reviewed under that NDA (John Jessop, Reviewer; review stamp-dated ~9/16/97).

For the new route of administration (intranasal) in the current application, new carcinogenicity studies were not required. However, additional general toxicology studies were/are required to determine local toxicity due to the intranasal route. Review of the 6-mo intranasal study of degraded zolmitriptan in rats did not reveal any cancerous or precancerous findings in the nasal cavity, respiratory tract, eyes, or associated lymph nodes.

Labeling Recommendations: Expanded from labeling for Zomig tablets and Zomig ZM™ orally disintegrating tablets:

"

[redacted]

"

✓ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

\ § 552(b)(5) Draft Labeling

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Zolmitriptan has been approved under NDA 20-768 for clinical use as an oral tablet; reproductive toxicology studies for zolmitriptan were reviewed under that NDA (John Jessop, Reviewer; review stamp-dated ~9/16/97).

The intranasal formulation contains 2 degradants whose specifications in the to-be-marketed product have been set above the threshold for qualification. According to the ICH Guidance for Industry, Q3B, Impurities in New Drug Products (11/1996), qualification of these degradants may require other studies (in addition to general toxicity and *in vitro* genotoxicity), as appropriate considering the patient population and duration of use. Because this intranasal formulation of zolmitriptan will be used in women of child-bearing potential, a Segment II study in one animal species was requested by the Division and provided by the Sponsor (see review, below).

Study title: Zolmitriptan: Teratology study in rats: oral administration.

Key study findings:

- **No major malformations up to HD (1000 mg/kg/d);**
- **Decreased maternal weight gain at HD;**
- **Doses of degradants at HD were: ——— for ———, and ——— for ———**
- **2-3-fold lower systemic exposures to zolmitriptan (and metabolites) than were achieved in the Segment II study that supported the oral formulations.**

Study no.: Zeneca Pharmaceuticals ref no. TTR/2980 (toxicology); ——— study no. 88/271 (analysis of PK samples).
Volume #, and page #: electronic submission 2/27/02: pharmtox\tox\repro\TTR2980.pdf (287 pages); ———, PK report in Appendix B on pages 55-106.
Conducting laboratory and location: Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, England (toxicology); ——— (analysis of PK samples).
Date of study initiation: 5/24/99 (start of dosing); through 6/8/99 (necropsy).
GLP compliance: yes, see page 2.
QA reports: yes, see pages 10-11.
Drug, lot #, and % purity: zolmitriptan ———; batch ref 5180, ——— no 02100198, manufactured 4/96, by ———, was formulated as a sterile solution (see vehicle, below) containing ——— w/v zolmitriptan (formulation batch ref no P/1468/32); HPLC assay (5/25/99) determined 45 mg/ml zolmitriptan and ———, total impurities, including ——— and ———
Formulation/vehicle: sterile solution containing ———, w/v citric acid (anhydrous), adjusted to pH 5 with sodium phosphate dodecahydrate.

Methods:

Species/strain: male and female AP rats (Alpk:ApfSD strain, Wistar-derived; from Zenaca's Rodent Breeding Unit, Alderley Park).
Doses employed: 0, 100, 400, and 1000 mg/kg/d po [NB Doses of 0, 100, 400, and 1200 mg/kg/d po were used in the study of (non-degraded) zolmiptriptan that was reviewed in support of NDA 20-768.]
Route of administration: oral gavage of placebo (2 ml/100 g/day) or the "50 mg/ml" (degraded) zolmitriptan solution (0.2, 0.8, or 2 ml/100 g/day for 100, 400, or 1000 mg/kg/day, respectively).
Study design: Mated female rats were dosed on days 7-16 of pregnancy; the day they were positive for sperm (i.e., 1 day after pairing) was counted as day 1 of pregnancy. Rats were killed for necropsy on day 22 of pregnancy.
Number/sex/group: 22 mated females per group; each female was paired with a different proven male for 1 day (during predicted estrus) and females with sperm-positive vaginal smear were used for the study.
Parameters and endpoints evaluated: Maternal variables: copora lutea (maternal ovaries) and pregnancy status, including uterus weight, implantation sites, resorption sites, live and dead fetuses (uterus). Fetal variables: all live fetuses were weighed, examined externally, sexed. Fetuses were then killed, grossly examined, kidneys and heart were examined for internal structure; all carcasses were stained with Alizarin Red S and fetal skeletons from control and HD were examined.

Results:

Maternal parameters:

Maternal mortality: None: all rats survived to scheduled termination on day 22 of pregnancy.

Maternal clinical signs: increased incidence of salivation at MD and HD during dosing.

Maternal body weight and food consumption: Body weights were recorded on day 1, 7, 10, 13, 16, 19, and 22, however, only body weight gains were provided in this study report. [Female rats were ~10-12 weeks old and weighed 223-294 g when received, 6 days before dosing started.] HDF gained 14% less weight than controls during the entire pregnancy (145 g, compared with 169 g) and 23% less during the dosing period (46 g, compared with 60 g). This decrease in body weight gain was especially prominent during days 7-10, when HDF gained 58% less than controls (8 g, compared with 19 g). At this early time in dosing, MDFs also gained less than controls (↓37%; 12 g, compared with 19 g), however, their total weight gain during pregnancy or during dosing was not affected. The decreased weight gain in the HDFs was accompanied by a slight (~10%, non-significant) decrease in weekly food consumption during dosing.

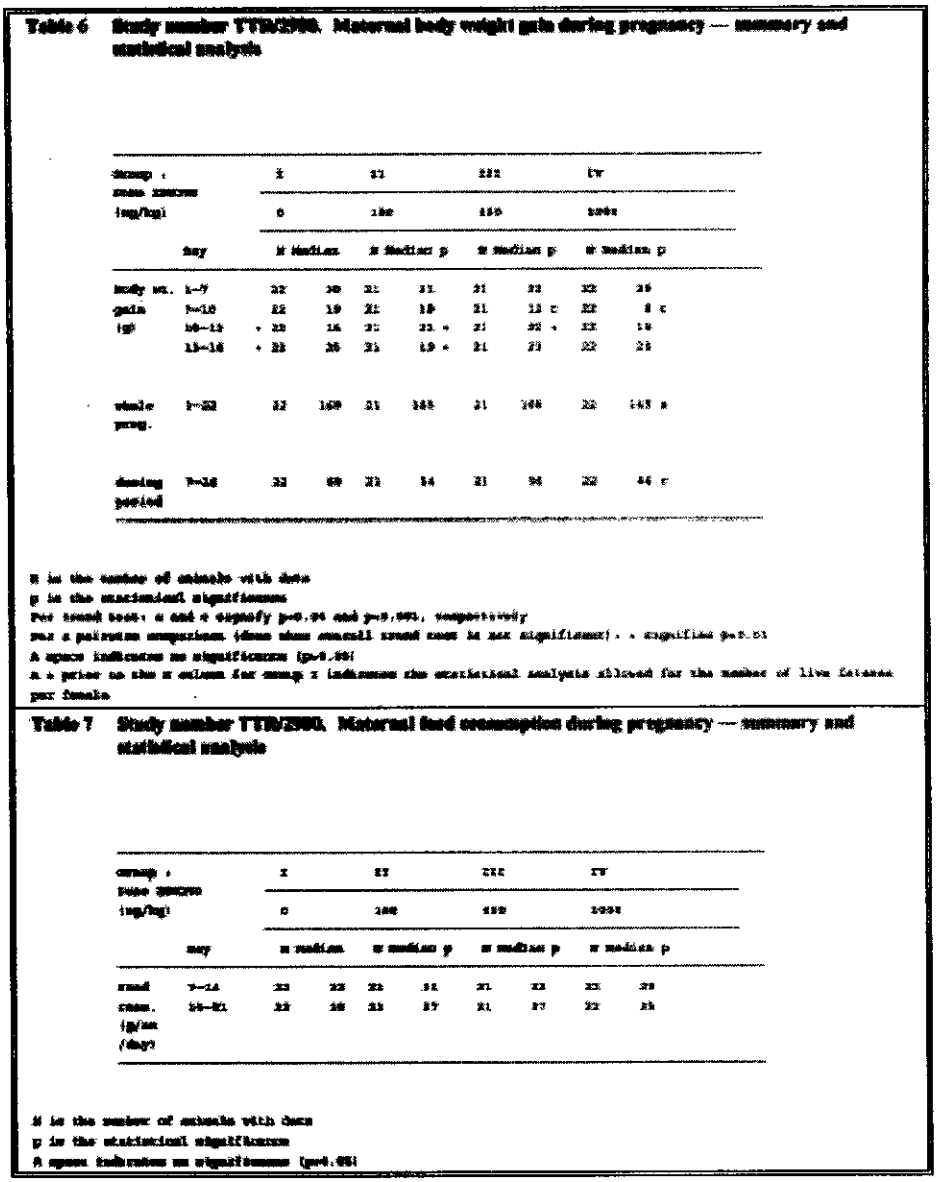

Table 6 [illegible]

Group :	1		11		111		IV	
mmm mmmm (mg/kg)	0		100		300		1000	
Day	N	Median	N	Median p	N	Median p	N	Median p
Body wt. gain (g)	1-7	22	20	21	21	21	22	20
	7-10	22	19	21	19	21	22 c	8 c
	10-13	22	16	21	23	21	22	16
	13-16	22	25	21	19	21	22	23
whole preg.	1-22	22	109	21	103	21	22	103 a
during period	7-16	22	69	21	54	21	22	44 c

N is the number of animals with data
p is the statistical significance
For trend test: c and a signify p<0.05 and p<0.001, respectively
For a pairwise comparison (does that overall trend come in any significance) : a signifies p<0.01
A space indicates no significance (p>0.05)
A a prior to the n column for group 1 indicates the statistical analysis allowed for the number of live fetuses per female

Table 7 [illegible]

Group :	1		11		111		IV	
mmm mmmm (mg/kg)	0		100		300		1000	
Day	N	Median	N	Median p	N	Median p	N	Median p
Food cons. (g/an /day)	7-16	22	22	21	21	21	22	20
	16-21	22	20	21	20	21	22	21

N is the number of animals with data
p is the statistical significance
A space indicates no significance (p>0.05)

Maternal reproductive parameters: All but 1 (MD) female were pregnant. All but 1 (LD) female had live fetuses; that 1 LDF had only resorptions and is not included in the calculations in the table, below. There were no treatment effects on maternal variables; there was essentially no pre- or post-implantation loss.

Maternal variables for Segment II study of 0, 100, 400, and 1000 mg/kg oral (gavage) doses of zolmitriptan (degraded formulation) in rats. [Sponsor's table, excerpted directly from this submission, page 33.]

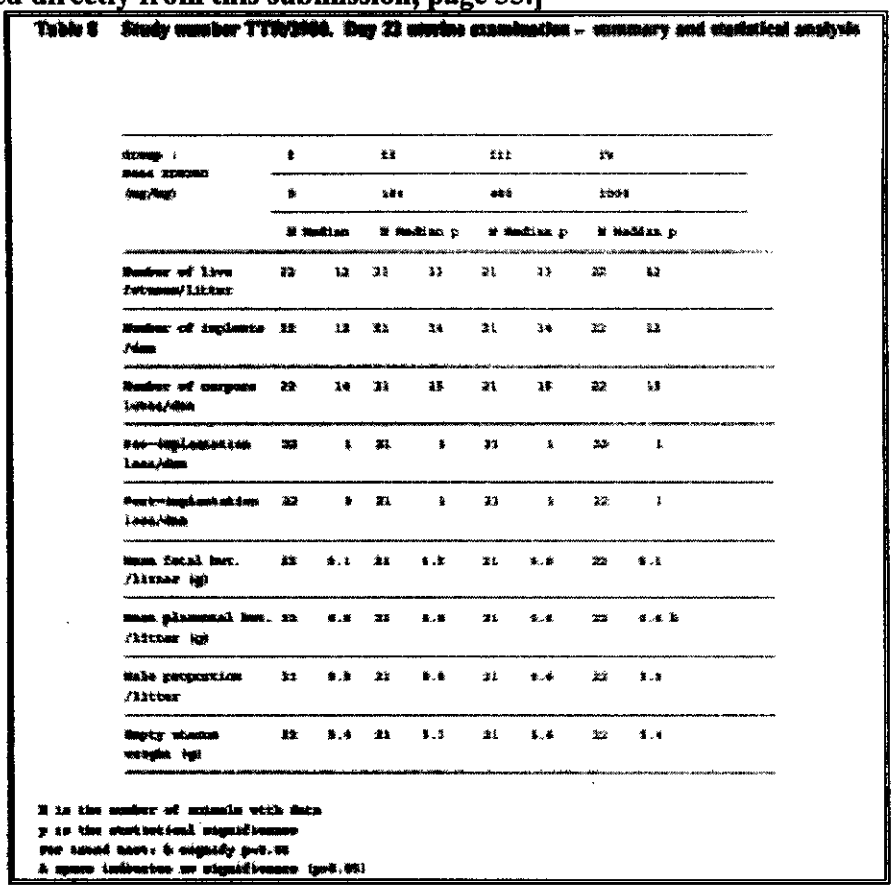

Table 6 Study number TT0/2000. Day 22 uterine examination – summary and statistical analysis

Group	I	II	III	IV
mean exposure (mg/kg)	0	100	400	1000
	N Median	N Median p	N Median p	N Median p
Number of live fetuses/litter	22 12	21 13	21 13	22 12
Number of implants /dam	22 13	21 14	21 14	22 13
Number of corpora lutea/dam	22 14	21 15	21 15	22 13
Pre-implantation loss/dam	22 1	21 1	21 1	22 1
Post-implantation loss/dam	22 0	21 1	21 1	22 1
Mean fetal bwt. /litter (g)	22 6.1	21 6.2	21 6.0	22 6.1
mean placental bwt. /litter (g)	22 0.6	21 0.6	21 0.6	22 0.6 b
Male proportion /litter	21 0.5	21 0.6	21 0.6	22 0.5
Empty uterus weight (g)	22 0.6	21 0.5	21 0.6	22 0.6

N is the number of animals with data
p is the statistical significance
for trend test: b signify p<0.05
A space indicates no significance (p>0.05)

Maternal toxicokinetics: The AUC exposures calculated for zolmitriptan in the current study (see table, below) demonstrate exposure to the drug (and presumably the degradants). However, the actual AUCs achieved (for zolmitriptan and metabolites) in this study are (2-3-fold) lower than those for comparable doses of (non-degraded) zolmitriptan in the Segment II rat study that supported NDA 20-768 (as reviewed by J. Jessup, see Sponsor's table, below).

Table 3 Study number TTH/2000. Mean plasma concentrations (ng/ml) and AUC_{0-8} (ng.h/ml) for zolmitriptan and its 3 major metabolites

		Zolmitriptan		183C91		1652W92		2161W92	
Group	Time (h)	Mean	SD	Mean	SD	Mean	SD	Mean	SD
II	2	2924	950	107	11.8	144	43.4	435	85.5
	4	1718	679	79.3	17.7	90.8	37.2	280	122
	6	1649	768	59.5	25.0	66.4	20.9	209	113
	8	1082	65.4	46.3	14.1	46.6	5.61	146	26.0
	AUC_{0-8}	10740		431		505		1560	
III	2	12077	2919	192	46.7	320	44.5	895	253
	4	10446	1808	174	43.1	325	55.7	635	78.6
	6	10247	2037	184	13.7	357	67.0	738	59.4
	8	6990	1273	136	30.7	278	77.1	541	138
	AUC_{0-8}	60052		1044		1961		4184	
IV	2	31204	7470	442	106	615	146	1256	150
	4	31211	5738	434	57.9	927	18.1	1587	296
	6	30344	5816	417	88.9	850	119	1601	431
	8	22648	5209	254	32.1	623	96.5	1160	231
	AUC_{0-8}	176961		2398		4790		8792	

SD Standard deviation

Exposures to zolmitriptan and 3 metabolites from the Segment II rat study that supported NDA 20-768 for the oral formulations of zolmitriptan. [Excerpted directly from J. Jessup's review of that NDA.]

Pharmacokinetics

Profiles were taken on Days 6 and 15 for both parent 311C90 and its metabolites (1652W92, 183C91 and 2161W92).

	311C90 (mg/kg/day)			
	Control	100	400	1200
311C90 Day 6				
$AUC_{0-\infty}$	-	29.2	114.4	255.4[a]
Cmax	-			
Day 15				
AUC_{0-24}	-	33.3	133.8	604.9
Cmax	-			
1652W92 Day 6				
$AUC_{0-\infty}$	-	1.9	5.6	11.9
Cmax	-			
Day 15				
AUC_{0-24}	-	1.3	4.0	21.6
Cmax	-			
183C91 Day 6				
$AUC_{0-\infty}$	-	1.1	3.1	6.9
Cmax	-			
Day 15				
AUC_{0-24}	-	1.7	4.8	18.2
Cmax	-			
2161W92 Day 6				
$AUC_{0-\infty}$	-	3.2	9.4	18.6
Cmax	-			
Day 15				
AUC_{0-24}	-	4.0	9.3	24.9
Cmax	-			

AUC (µg/ml x h) — area under the plasma concentration–time curve

[a] AUC_{0-24} (µg/ml x h) — area under the plasma concentration–time curve for the daily dose

Cmax (µg/ml) — maximum observed plasma concentration

Fetal parameters:

Fetal weights: Drug-treatment did not alter fetal body weights, which averaged ~ 5 g for all groups.

Embryo/fetal variables for Segment II study of 0, 100, 400, and 1000 mg/kg oral (gavage) doses of zolmitriptan (degraded formulation) in rats. [Sponsor's values.]

PARAMETER	DOSE, mg/kg/d (gestational D6-17)			
	0	100	400	1000
Mean live fetuses/litter	12	13	13	12
Mean proportion males per litter	0.5	0.6	0.6	0.5
Mean fetus weights, g	5.1	5.2	5.0	5.1
Total litters examined	22	21	21	22
Total fetuses examined for external abnormalities	~260	~240	~270	~240
Total fetuses examined for visceral abnormalities	~260	~240	~270	~240
Total fetuses examined for skeletal abnormalities	~260	0	0	~240
Total fetuses with malformations	0	0	0	0

Fetal terminal and necroscopic evaluations: The only external/visceral defects were in the ureter (see table, below). Fetuses from drug-treated dams showed a higher incidence of kinked ureter, without apparent dose-dependency; this defect occurred in 0.8% of control fetuses (9% of control litters) and 3-6% of drug-treated fetuses (24-43% of drug-treated litters). In contrast, the severity of dilated ureter was less in drug-treated fetuses (fewer moderate) than in controls. Skeletal examination of all control and HD fetuses revealed several incomplete ossifications, but the incidence of these in HD fetuses was equal to or less than that in controls; with the possible exception of incomplete supra-occipital ossification of the skull, where there was a slightly greater incidence in HD fetuses (73%) compared with control fetuses (63%), however, this defect was present in essentially all control (100%) and HD (96%) litters.

Visceral findings for Segment II study of 0, 100, 400, and 1000 mg/kg oral (gavage) doses of zolmitriptan (degraded formulation) in rats. [From Sponsor's summary table, excerpted directly from this submission, page 34.]

Table 9 Study number TTR/2980. Summary of findings from fetal external, visceral and skeletal examinations

	GROUP 1 0 mg/kg		GROUP 2 100 mg/kg		GROUP 3 400 mg/kg		GROUP 4 1000 mg/kg	
	CLASS		INCIDENCE BY FOETUS/LITTER					
	NO.	%	NO.	%	NO.	%	NO	%
URETER								
DILATED - MODERATE	F	(3.4)	1	(0.4)	4	(1.5)	3	(1.3)
	6	(27.3)	1	(4.8)	3	(14.3)	3	(13.6)
DILATED - SLIGHT	2	(0.8)	6	(2.5)	9*	(3.3)	4	(1.7)
	2	(9.1)	4	(19.0)	6	(28.6)	3	(13.6)
KINKED	2	(0.8)	15**	(6.3)	20*	(7.7)	7	(3.0)
	2	(9.1)	9*	(42.9)	5	(23.8)	6	(27.3)

Reproductive and developmental toxicology summary: There were no major external, visceral, or skeletal abnormalities at oral doses of degraded zolmitriptan formulation up to 1000 mg/kg/d, a dose that decreased maternal body weight gain.

This HD (1000 mg/kg) gives safety margins for zolmitriptan of 5900 and 970 for the maximum recommended human daily dose of 10 mg (i.e., 0.17 mg/kg and 6.2 mg/m^2 for a 60 kg human) on a mg/kg and mg/ m^2 basis, respectively. However, the exposures to zolmitriptan (and metabolites) in this oral study were 2-3-fold lower than those achieved in the oral Segment II study that supported the oral formulations. [The HD of degraded zolmitriptan used in the current study was 1000 mg/kg, compared with a HD of 1200 mg/kg of non-degraded zolmitriptan used in the earlier study.] The safety margins for the doses of the 2 degradants ' _____ , are at least as great as for zolmitriptan, because the percentages of the degradants in formulation used in this study are greater than the specifications for the to-be-marketed formulation.

Reproductive and developmental toxicology conclusions: This study is adequate for qualification of the 2 degradants _____ . Safety margins for the degradants are at least as great as for zolmitriptan (i.e., at least 5900 and 970 for the maximum recommended human daily dose of 10 mg on a mg/kg and mg/ m^2 basis, respectively). However, the negative results should not be used in labeling, because the systemic doses and exposures for zolmitriptan are lower than those in the study that supported labeling for the oral formulations.

Labeling recommendations: PRECAUTIONS/Impairment of Fertility: Not changed from labeling for Zomig tablets and Zomig ZM™ orally disintegrating tablets.

Labeling recommendations: PRECAUTIONS/Pregnancy:Pregnancy Category C: Changed/expanded from labeling for Zomig tablets and Zomig ZM™ orally disintegrating tablets:

"

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

VIII. SPECIAL TOXICOLOGY STUDIES:

Study title: [Degraded] Zomig nasal spray 50 mg/ml: eye irritation study in rabbits.

Key study findings:

- **Dose was 0.1 ml (degraded "Zomig nasal spray 50 mg/ml," containing 43 mg/ml zolmitriptan and — degradant — and — degradant —) to single eye;**
- **Slight, transient redness of cornea;**
- **No effects on cornea or iris.**

Study no: — study no FB5653; Zenaca Pharmaceuticals ref no. AH/98/001.
Volume #, and page #: electronic submission 2/27/02: pharmtox\tox\special\FB5653.pdf (35 pages).
Conducting laboratory and location: —, Sponsor: Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK.
Date of study initiation: 4/15/98 (experimental phase).
GLP compliance: yes, see page 3.
QA reports: yes, see page 5.
Drug, lot #, and % purity: [degraded] Zomig nasal spray 50mg/ml; — batch ref no. PH/10828/26, — no. 01945A98; Certificate of Analysis for initial sample noted pH 5.2, assayed (HPLC, 6/19/98) at — zolmitriptan and containing —w/w total degradants (HPLC), including — w/w — and —; an end of study sample (pH 5.2) analyzed (HPLC, 6/19/98) at — zolmitriptan, with — total HPLC impurities, including — w/w — and —.
Formulation/vehicle: Zomig nasal spray 50 mg/ml, pH 5.2.

Methods: 3 young adult, male New Zealand White albino rabbits — weighing 2887-3863g at beginning of study, were individually housed with food and water *ad libitum*, with 12 hr/12 hr light/dark cycle.

Dosing: Test article (0.1 ml; degraded Zomig nasal spray) was instilled into the conjunctival sac or the left eye by gently pulling the lower lid away from the eyeball; the lids were then gently held together for 1-2 sec; the right eye was untreated and served as the control.

Observations and times: Both eyes were examined (visual assessment with fluorescein) the day before dosing, to verify absence of eye defects or ocular irritation. After drug administration, initial pain response was graded and both eyes were examined at 1 hr, and 1, 2, and 3 days, using the Draize scale to grade the ocular reaction; this scale grades cornea, iris, and conjunctivae.

Results: Instillation of 0.1 ml of degraded formulation of Zomig nasal spray caused no pain (i.e., no initial response) in 2/3 rabbits and practically no initial pain (i.e., a few blinks only; normal within one or two minutes). There were no effects on cornea (no opacity) or iris (normal reaction to light, no congestion, swelling, circumcorneal injection, hemorrhage, or gross destruction). Findings in conjunctiva were transient and slight: 2/3 displayed slight redness ~1 hr after dosing only; the third displayed slight redness 1 day after dosing only. There was no swelling and no discharge.

Conclusions: 0.1 ml of degraded formulation produced only a transient, slight redness in the conjunctiva, with no adverse effects on cornea or iris with examination up to 3 days after dosing.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

A. Overall Summary and Conclusions:

Pharmacodynamics: This NDA relies upon the pharmacodynamic studies that supported the approval of the oral formulations. The pharmacology studies for zolmitriptan were reviewed under NDA 20-768; no new pharmacology studies were submitted in the current NDA. Briefly, based upon the Review of NDA 20-768, zolmitriptan is a high affinity agonist at 5-HT1D serotonin receptors (pKi ~9), but also has "...reasonably high affinity for the 5-HT1A receptor (pKi 7.0), which is thought to mediate CNS side effects, among others."

Safety Pharmacology: This NDA relies upon the safety pharmacology studies that supported the approval of the oral formulations. The safety pharmacology studies for zolmitriptan were reviewed under NDA 20-768; no new pharmacology studies were submitted in the current NDA. In brief, preclinical studies indicated that zolmitriptan had a potential for cardiovascular side effects. It increased blood pressure and heart rate in conscious dogs. It also resulted in a concentration-related contraction of human coronary artery *in vitro*; "this may be of some concern, as coronary vasospasm is one of the undesirable side effects of sumatriptan." The active human metabolite 183C91 was considered to be adequately examined for pharmacology and safety pharmacology.

Pharmacokinetics: The pharmacokinetic data from human studies comparing the intranasal and oral routes demonstrated that there was no increase in systemic exposures to zolmitriptan or its major metabolites; and no new metabolites were identified. Consequently, although the Sponsor submitted several studies investigating the PK/TK of intranasal zolmitriptan in animals, these studies were not considered necessary to support the current NDA submission and have not been reviewed here; however, PK data was reviewed with toxicology studies, where relevant.

General Toxicology: This NDA relies upon the general oral toxicity studies that supported the approval of the oral formulations. Additionally, new studies using degraded formulations, containing greater percentages of the new degradants than the specifications for the to-be-marketed formulation, were provided to satisfy the requirements for both the change in formulation and the qualification of the new degradants. Local toxicity was determined with degraded formulation in 1-mo studies in rats and monkeys and in a 6-mo study in rats. In terms of degradant qualification, the local toxicity studies using the degraded formulation satisfy the requirement for repeated-dose toxicity testing, because systemic exposures were adequate, maximum feasible doses were used, and general toxicity analysis was performed, including full histopathology.

[In these studies, the Sponsor estimated local doses of zolmitriptan based upon values for surface areas of nasal cavity in different species from a book chapter authored by J. P. Schreider (In: *Nasal Tumors in Animals and Man*, vol III, *Experimental Nasal Carcinogenesis*, CRC Press, Boca Raton, FL, 1983). I calculated the local dose for humans from the maximum recommended daily human dose of 10 mg, correcting the 181 cm^2 surface area listed in that reference for a 70 kg human to 160 cm^2 for a 60 kg human; the estimated local human dose for 10 mg/60 kg/day is 0.062 mg/cm^2.]

There was no local or general toxicity in monkeys given maximally feasible intranasal doses of degraded formulation up to ~64 mg/kg/d for 1 month. This dose is 380-times or 71-times the maximum recommended human daily dose of 10 mg on a mg/kg or mg/m^2 basis, respectively. The estimated local dose is 120-times the estimated local human dose (of 0.062 mg/m^2).

Non-degraded zolmitriptan administered intranasally at doses up to 72 mg/kg/d to rats for 1 month resulted in dose- and time-related behavioral responses, including paddling, squinting, and salivation. Decreased weight gain and food consumption was seen in HD males. Additionally, there was some indication of local irritation, with minimal to slight rhinitis in MD males (36 mg/kg/d) and HD males and females; and minimal nasopharyngitis in HD males and females. These findings were at least partly replicated using intranasal administration of non-degraded and degraded formulations in a 1-month rat study. The behavioral responses and minimal to slight rhinitis were seen in rats given both degraded and non-degraded zolmitriptan; however, no suppression of body weight gain was apparent.

In contrast, there was no local toxicity in rats given maximally feasible intranasal doses of degraded zolmitriptan formulation up to HD of ~72 mg/kg/d for 6 months. Specifically there was no increased incidence of rhinitis as had been seen in the 1-month studies. Additionally, there were no cancerous or precancerous lesions related to the intranasal route, in the nasal cavity, respiratory tract, eyes, or associated lymph nodes. General toxicity was limited to behavioral responses similar to those seen 1-month studies. Systemic exposures to zolmitriptan were ~ half those achieved in the 2-yr rat (oral) carcinogenicity that supported the approval of the oral formulations. The HD of 72 mg/kg is 420-times or 68-times the maximum recommended human daily dose of 10 mg on a mg/kg or mg/m^2 basis, respectively. The estimated local dose is 21-times or 32-times the estimated local human dose (of 0.062 mg/m^2) for male and female rats, respectively.

It should be noted that the safety margins for the 2 degradants being qualified ——— and ———, are at least as great as those for zolmitriptan, because the percentage of each degradant in the degraded formulations used in the pivotal preclinical studies was always greater than the specification for that degradant in the to-be-marketed formulation.

In conclusion, the 1-mo studies in rats and monkeys and the 6-mo study in rats where degraded zolmitriptan was administered intranasally support both the change in route of administration (from oral to intranasal) and the qualification of the 2 new degradants,

——— and ——— . There was no new general or local toxicity associated with the change in route or presence of the degradants.

Genotoxicity: This NDA relies upon the genetic toxicity studies that supported the approval of the oral formulations. Additionally, new studies were performed to qualify the 2 new degradants (———————), using degraded formulations containing greater percentages of these degradants than the specifications for the to-be-marketed formulation. Degraded zolmitriptan formulations were tested for *in vitro* mutagenicity (Ames test) and *in vitro* clastogenicity (human lymphocyte assay). Degraded nasal spray formulation was negative in a valid Ames test. The *in vitro* clastogenicity was similar for degraded and non-degraded formulations in the human lymphocyte assay; this *in vitro* clastogenicity was also seen for non-degraded zolmitriptan in the study that supported the approval of the oral formulations. Additionally, the degraded formulation was negative in a mouse micronucleus assay; this had been found to be true for non-degraded zolmitriptan in a mouse micronucleus assay that supported the approval of the oral formulations. Finally, degraded and non-degraded zolmitriptan were determined to be negative in a definitive rat micronucleus assay.

In conclusion, these new genotoxicity studies with degraded formulations are adequate to support qualification of the 2 new impurities, ——— and ———

Carcinogenicity: This NDA relies upon the 2-year oral carcinogenicity studies in rats and mice that supported the approval of the oral formulations. For the new route of administration (intranasal) in the current application, new carcinogenicity studies were not required. However, additional general toxicology studies were required to determine local toxicity due to the intranasal route. Review of the 6-mo intranasal study of degraded zolmitriptan in rats did not reveal any new concerns for carcinogenicity due to the nasal route of administration, at estimated local (nasal cavity surface area) doses that are 120-fold those estimated for humans at the maximum recommended human daily dose of 10 mg.

Reproductive Toxicity: This NDA relies upon the oral reproductive toxicity studies that supported the approval of the oral formulations. In addition, to qualify the 2 new degradants (——— and ———), the Sponsor submitted an oral Segment II study in rats using degraded nasal spray formulation with concentrations of these 2 degradants above the specification for the to-be-marketed formulation.

In this new Segment II study, there were no major external, visceral, or skeletal abnormalities at oral doses of degraded zolmitriptan formulation up to 1000 mg/kg/d, a dose that decreased maternal body weight gain (maximum tolerated dose).

This HD (1000 mg/kg) gives safety margins for systemic doses of zolmitriptan of 5900 and 970 for the maximum recommended human daily dose of 10 mg (i.e., 0.17 mg/kg and 6.2 mg/m^2 for a 60 kg human) on a mg/kg and mg/ m^2 basis, respectively. However,

the systemic exposures to zolmitriptan (and metabolites) in this oral study were 2-3-fold lower than those achieved in the oral Segment II study that supported the oral formulations. [The HD of degraded zolmitriptan used in the current study was 1000 mg/kg, compared with a HD of 1200 mg/kg of non-degraded zolmitriptan used in the earlier study.]

The safety margins for the systemic doses of the 2 degradants (——— and ———) are at least as great as for zolmitriptan, because the percentages of the degradants in the degraded formulation used in this study are greater than the specifications for the to-be-marketed formulation.

In conclusion, this study is adequate for qualification of the 2 degradants (——— and ———). Safety margins for the degradants are at least as great as for zolmitriptan (i.e., at least 5900 and 970 for the maximum recommended human daily dose of 10 mg on a mg/kg and mg/ m^2 basis, respectively). However, the negative results should not be used in labeling, because the systemic doses and exposures for zolmitriptan were lower than those in the study that supported labeling for the oral formulations.

B. Pharmacology/Toxicology Issues and Recommendations:

There are no further pharmacology/toxicology concerns for this NDA. There are no new preclinical concerns related to the nasal route of administration or attributable to the presence of the 2 new degradants ——— that required qualification.

C. Recommendations for Labeling:

[See individual sections of this review for justifications for changes to Sponsor's proposed labeling.]

CLINICAL PHARMACOLOGY/Mechanism of Action: Accept Sponsor's labeling, which is the same as the existing labeling for oral formulations.

Clinical Phamacokinetics and Bioavailability/Metabolism: ———

WARNINGS/Local Adverse Reactions: ———

PRECAUTIONS/Binding to Melanin-containing Tissues: Accept Sponsor's labeling including insertion of lack of effect on retina in intranasal animal studies; existing labeling for oral formulations includes this information for oral animal studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Carcinogenesis:

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Mutagenesis: . Include negative results in rat micronucleus assay. Recommended labeling below:

Mutagenesis: Zolmitriptan was mutagenic in an Ames test, in 2 of 5 strains of S. typhimurium tested, in the presence of, but not in the absence of, metabolic activation. It was not mutagenic in an *in vitro* mammalian gene cell mutation (CHO/HGPRT) assay. Zolmitriptan was clastogenic in an *in vitro* human lymphocyte assay both in the absence of and the presence of metabolic activation. Zolmitriptan was not clastogenic in *in vivo* mouse and rat micronucleus assays. Zolmitriptan was not genotoxic in an unscheduled DNA synthesis study.

Carcinogenesis, Mutagenesis, Impairment of Fertility/ Impairment of Fertility: Accept Sponsor's labeling which is the same as the existing labeling for the oral formulations.

Pregnancy: Pregnancy Category C: . Recommended labeling (existing labeling for oral formulations) below:

Pregnancy: Pregnancy Category C: There are no adequate and well controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals was associated with embryolethality and fetal abnormalities. When pregnant rats were administered oral zolmitriptan during the period of organogenesis at doses of 100, 400, and 1,200 mg/kg/day, there was a dose-related increase in embryolethality which became statistically significant at the high dose. The maternal plasma exposures at these doses were approximately 280, 1,100, and 5,000 times the exposure in humans receiving the maximum recommended total daily dose of 10 mg. The high dose was maternally toxic, as evidenced by a decreased maternal body weight gain during gestation. In a similar study in rabbits, embryolethality was increased at the maternally toxic doses of 10 and 30 mg/kg/day (maternal plasma exposures equivalent to 11 and 42 times exposure in humans receiving the maximum recommended total daily dose of 10 mg), and increased incidences of fetal malformations (fused sternebrae, rib anomalies) and variations (major blood vessel variations, irregular ossification pattern of ribs) were observed at 30 mg/kg/day. Three mg/kg/day was a no effect dose (equivalent to human exposure at a dose of 10 mg). When female rats were given zolmitriptan during gestation, parturition, and lactation, an increased incidence of hydronephrosis was found

in the offspring at the maternally toxic dose of 400 mg/kg/day (1,100 times human exposure).

X. APPENDIX/ATTACHMENTS:

Appendix A

A brief summary of the history of preclinical issues with IND 53,848 for the nasal formulation of zolmitriptan.

Early in development it was determined that the intranasal formulation contained a degradant ——— that was not present in the approved tablet formulation and required qualification. The IND (53,848) was placed on Clinical Hold from it's initial submission (9/4/97) until acceptable qualification studies were submitted/reviewed (Response to Hold, N-006, 6/17/99). Although the 1-month intranasal bridging studies in rats and monkeys submitted in the Response to Hold were considered adequate, the Clinical Hold was not lifted at that time, due to emergence of another issue. The Sponsor had also submitted the report for an oral *in vivo* micronucleus test of degraded zolmitriptan formulation in male rats (N-005, 6/17/99) and the results were arguably positive. [There was a very low, but dose-related increase in micronuclei in (male) rats treated with the degraded formulation for 48, but not 24 hr. It should be noted that the negative control was 0, with no range (i.e., there was no measurable incidence in any controls), and the highest value for the degraded formulation of zolmitriptan (1000 mg/kg) was only ——— per rats, with a range of —] This was deemed of great enough concern to keep the IND on clinical hold, presumably because the benefit of this new formulation of an already-approved drug was not deemed to out-weigh the potential, new genotoxicity. [NB Undegraded zolmitriptan was negative in a mouse micronucleus assay under NDA 20-768.]

Subsequently, study reports of several additional *in vivo* micronucleus assays were submitted (N-020, 4/19/01), in an attempt to clarify the significance of the earlier results that occasioned the continuation of the Clinical Hold. This Reviewer agreed with the Sponsor that when an adequate number of cells (PEs) were counted to obtain a measurable incidence of micronuclei in most control rats, zolmitriptan (degraded or undegraded) was negative in the rat micronucleus assay. In this same submission, the Sponsor included the results of a mouse micronucleus assay using degraded zolmitriptan; the initial test was arguably positive for females at 48 hr, but this result did not repeat; this Reviewer considered the results of this study to be negative. [More details of these micronucleus study results can be found in the body of this review, Section V. Genetic Toxicity, Subsection C. *In vivo* clastogencity.]

In a June 19, 2001, meeting with the Sponsor, it was agreed that:

> "A full response to Clinical Hold should include:
> 1. justification of the oral route for the *in vivo* micronucleus assay; or
> 2. an *in vitro* chromosomal aberration assay comparing the non-degraded and degraded formulations; or
> 3. a carcinogenicity study, either standard or using an alternative model (e.g., p53)."

In a subsequent Response to Hold submission (N-025, 12/1/01), the Sponsor provided the study report for an *in vitro* chromosomal aberration assay comparing the non-degraded

and degraded formulations (see option #2, above). Additionally, the Sponsor provided a table showing the amounts of degradant [redacted], as well as of 3 other degradants that might be present in the clinical formulation, in the preclinical studies that have been performed to qualify degradant(s). Review of this submission determined that the degraded formulation was no more clastogenic than the non-degraded formulation in the *in vitro* chromosomal aberration test and that this satisfied the requirements set forth by the Division (see above) to lift the clinical hold.

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/s/

Linda Fossom
12/18/02 01:15:47 PM
PHARMACOLOGIST

Barry Rosloff
12/19/02 12:31:15 PM
PHARMACOLOGIST