CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022388Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	022388
Supporting document/s:	SDN001
Applicant's letter date:	4-30-2021
CDER stamp date:	4-30-2021
Product:	Acuvue Theravision with ketotifen (Etafilcon A lens with ketotifen)
Indication:	For correcting refractive ametropia (myopia and hyperopia) in phakic or aphakic patients who are suitable for contact lens wear and experience ocular allergic itch due to allergic conjunctivitis and who do not have red eye(s) or more than 1.00 D of astigmatism.
Applicant:	Johnson and Johnson Vision Care Inc. (Jacksonville, FL 32256)
Clinical Review Division:	Division of Ophthalmology (DO)
Pharm Tox Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURM/SM)
Reviewer:	Erin Ruhland, PhD
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1 Executive Summary

1.1 Introduction

The Applicant proposes “Acuvue Theravision with ketotifen”, a drug:device combination product, for correcting refractive ametropia (myopia and hyperopia) in phakic or aphakic patients who are suitable for contact lens wear and experience ocular allergic itch due to allergic conjunctivitis and who do not have red eye(s) or more than 1.00 D of astigmatism. The device component of K-Lens is the etafilcon A daily disposable contact lens, marketed as 1•DAY ACUVUE® Brand Contact Lens (etafilcon A) for single use daily disposable wear (marketed under 510k, Number: K013973, 2002b). Each contact lens contains 0.019 mg ketotifen fumarate as the active pharmaceutical ingredient.

The Applicant conducted nonclinical ocular toxicity studies to support the ocular safety of the proposed drug:device. The Applicant has filed a 505(b)(2) NDA with reliance on NDA 021066 (Zaditor®; Alcon Research Ltd) for aspects of nonclinical systemic safety of ketotifen fumarate. An adequate bridge for systemic safety is established by a large dose margin between API doses used in those studies relied upon and the content of the API in the drug:device. Zaditor® received an “Efficacy-Rx to OTC switch” approval on 10/19/2006.

1.2 Brief Discussion of Nonclinical Findings

- The Acuvue K-lens containing up to 0.038 mg ketotifen per lens (2x proposed formulation content) was not associated with ocular toxicity in rabbits administered the lens once daily for 6 months. Slight ocular irritation of the lens (and placebo lens) was indicated by conjunctival redness and slight lymphocytic infiltrates.
- The novel excipient, (b) (4) was qualified as non-genotoxic in *in vitro* assays and showed no signs of toxicity in rabbits following ocular instillation of the lens.

1.3 Recommendations

1.3.1 Approvability

- NDA 022388 is approvable from a Pharmacology/Toxicology discipline viewpoint .

1.3.3 Labeling

1.3.3.1 Applicant’s Version of Labeling (Sections 8, 12.1, and 13 only)

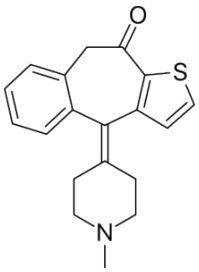
8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

2 Drug Information

2.1 Drug

Type of Product:	Drug:Device combination (contact lens stored in packing solution containing API)
Code/ Generic Name:	Acuvue Theravision with ketotifen (Etafilcon A lens with ketotifen)
Chemical Name (ketotifen):	4-(1-methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one
CAS# or UNII (ketotifen):	CAS:34580-14-8 UNII:HBD503WORO
Structure:	
Molecular Formula/ Molecular Weight:	$C_{19}H_{19}NOS$ / 309.43 g/mol
Comment on Excipients:	See below.
Proposed 505(b)(2): If Yes, Listed Drug:	Yes NDA 021066: Zaditor®
Biosimilar:	No

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 66,883 (formerly held by Vistakon Pharmaceuticals).
- NDA 021066: Zaditor® (ketotifen fumarate ophthalmic solution, 0.025%); Alcon Pharma
    - Approved: 7-2-1999
    - Indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.
    - Discontinued and not available as OTC: see ANDA 077200 .
    - No Pharmacology/Toxicology reviews were available online.
    - The maximum recommended human ocular dose used in the labeling (prior to OTC switch) was 0.0015 mg/kg/day on a mg/kg basis.

2.3 Drug Formulation

The drug component, ketotifen fumarate, is introduced via a buffered package solution (buffered ketotifen solution - BKS). The drug:device product is formed by combining the device component (etafilcon A soft contact lens) with the BKS (b) (4)

(b) (4) A concentration of 43 µg/mL of ketotifen fumarate in the primary package solution ensures nominal uptake of 0.019 mg of ketotifen/lens. The drug diffuses from the lens (b) (4) once the lens is inserted onto the cornea.

Composition of the Buffered Ketotifen Solution (BKS)

(b) (4)	% w/w
Ketotifen fumarate	0.0043
(b) (4) (b) (4))	(b) (4)
Calcium hydroxide	
Sodium chloride	
(b) (4)	
Boric acid	
Purified water	

2.4 Comments on Novel Excipients

(b) (4)

- The novel excipient, (b) (4) (b) (4) was qualified for ocular and systemic safety up to (b) (4) % in the packaging solution for the drug products used in the 6-month ocular toxicity study conducted in rabbits. Additionally, genotoxicity studies conducted with (b) (4) demonstrated that it was nonmutagenic in an *in vitro* bacterial reverse mutation study conducted with and without metabolic activation to four strains of *Salmonella typhimurium* and to *Escherichia coli*. (b) (4) did not cause chromosome aberrations in Chinese Hamster Ovary (CHO) cells up to 4690 µg/mL following 4-hour incubation with and without metabolic activation and up to 9.13 µg/mL following 20-hour incubation without metabolic activation.
- The uptake of (b) (4) into the K-Lens is negligible with virtually all of the (b) (4) remaining in the buffered ketotifen package solution. As requested by the Agency at the End of the Phase 2 meeting (see Module 1.6.3 for End of Phase 2 FDA meeting minutes), the amount of (b) (4) in the K-Lens was measured and demonstrated to be less than (b) (4) mg.
- A similar compound, (b) (4) (b) (4) .

2.6 Proposed Clinical Population and Dosing Regimen

- The patient is instructed to insert one lens per day to be removed prior to sleeping and no more than one lens should be used per day. The lens should be discarded after a single day's use.
- The daily dose, assuming complete absorption of the ketotifen from the lens, would be 0.019 mg/eye/day or 0.038 mg total daily dose if used bilaterally.

2.7 Regulatory Background

- Clinical studies were conducted under IND 66,883.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

- Study CR-4412: Evaluation of 1-day Acuvue® contact lens with ketotifen fumarate in packing solution: Determination of irritation and safety and preliminary of onset and duration of effect in the rabbit
- Study CR-4419: Evaluation of 1-day Acuvue® contact lens with ketotifen fumarate in packing solution: Evaluation of onset and duration of effect in the rabbit

Toxicology

- Study 08T_25208-04-05-06: Bacterial reverse mutation assay (b) (4)
- Study 08T_25208-02-03-07-08: Genotoxicity: *In vitro* chromosomal aberration study in mammalian cells
- Study 07T-44476-02: Six month ocular irritation and toxicity study in the rabbit

Pharmacokinetics

- Study CVV00001-05_05_1136: Assessment of binding of test compound to melanin (ketotifen fumarate)

3.2 Studies Not Reviewed

- Study 05T_33650_06: Genotoxicity: Bacterial reverse mutation study (Saline extract)
- Study 05T_33650_07: Genotoxicity: Bacterial reverse mutation study (DMSO extract)
- Study 05T_33651_06: Genotoxicity: Bacterial reverse mutation study (Saline extract)
- Study 05T_33651_07: Genotoxicity: Bacterial reverse mutation study (DMSO extract)
- Study 04T_45494_01: Modified ISO contact lens/solution ocular irritation study following a 30 day lens wear
- Study 05T_33195-01: Modified ISO contact lens/solution ocular irritation study following a 30 day lens wear
- Study 17T_74519_01_02: ISO modified ocular irritation study in rabbits
- Study 05T_33650_04/05: Murine local lymph node assay (LLNA) (SC and DMSO extracts)

- Study 05T-42031-01: Murine local lymph node assay (LLNA) (DMSO extract)
- Study 05T_33651_04/05: Murine local lymph node assay (LLNA) (SC and DMSO extracts)
- Study 05t-42029-01: Murine local lymph node assay (LLNA) (DMSO extract)
- Study 09T_35672_01/02: ISO maximization study
- Study 04T_49686_01: Cytotoxicity study using the ISO agarose overlay method (solid)
- Study 04T_49689_01: Cytotoxicity study using the ISO agarose overlay method (solid)
- Study 05T_33650_01: Cytotoxicity study using the ISO agarose overlay method (solid)
- Study 05T_33651_01: Cytotoxicity study using the ISO agarose overlay method (solid)
- Study 05T_33650_02/03: ISO ocular irritation study extract
- Study 05T_33651_02/03: ISO ocular irritation study extract
- Study 07T_39026_02: Cytotoxicity study using the ISO agarose overlay method (solid)
- Study 07T_39026_03/04: ISO ocular irritation study - extract
- Study 07T_22535_01: Cytotoxicity study using the ISO agarose overlay method (solid)
- Study 07T_22535_02/03ISO ocular irritation study - extract
- Study 17T_74519_03: Cytotoxicity study using the ISO direct contact method

4 Pharmacology

4.1 Primary Pharmacology

Ketotifen is relatively selective, non-competitive histamine antagonist (H-1 receptor) and mast cell stabilizer. Ketotifen inhibits the release of mediators from cells involved in hypersensitivity reactions. Decreased chemotaxis and activation of eosinophils has also been demonstrated.

Reviewer's note: The Clinical Pharmacology section of the Zaditor® label reads:

Ketotifen is a relatively selective, non-competitive histamine antagonist (H1-receptor) and mast cell stabilizer. Ketotifen inhibits the release of mediators from cells involved in hypersensitivity reactions. Decreased chemotaxis and activation of eosinophils has also been demonstrated.

Activity Relevant to the Proposed Indication:

- Study CR-4412: Evaluation of 1-day Acuvue® contact lens with ketotifen fumarate in packing solution: Determination of irritation and safety and preliminary of onset and duration of effect in the rabbit

- Phase I
  - Male New Zealand White rabbits (6/treatment group) were treated unilaterally with lenses containing ketotifen fumarate 0.005% (K-Lens 50, 0.038 mg ketotifen/lens) or 0.025% (K-Lens 250, 0.19 mg ketotifen/lens), each with and without (b) (4) in the package solution, were evaluated for irritation potential. The contralateral eye was treated with a placebo lens.
    - Reviewer's note: (b) (4) is a (b) (4) and is not included in the final formulation. No pharmacology studies were performed with a packaging solution containing (b) (4)
  - The highest dose of ketotifen fumarate tested, K-Lens 250 (0.19 mg ketotifen/lens), produced clinically significant mydriasis (defined as greater than or equal to 0.5 mm increase in pupil diameter relative to the control eye), as well as behavioral changes (a tendency to guard the eye containing K-Lens 250 or shut it) considered indicative of irritation; however, no apparent toxic side effects were seen with K-Lens 50 (0.038 mg ketotifen/lens). Presence or absence of the package solution additive (b) (4) had no effect on the findings. Based on these findings, K-Lens 50 (0.038 mg ketotifen/lens) was non-irritating and a safe concentration to use in non-clinical efficacy studies.
- Phase II
  - Male New Zealand White rabbits (6/treatment group) were treated unilaterally with:
    - Group 1: K-Lens 50 (0.038 mg ketotifen/lens) with (b) (4) and placebo lens (1•DAY ACUVUE) in the other eye
    - Group 2: K-Lens 50 without (b) (4) in one eye and the placebo lens in the other eye
    - Group 3: ketotifen fumarate ophthalmic solution 0.025% in one eye and phosphate-buffered saline (PBS; placebo) in the other eye.
  - The study determined the effectiveness at preventing the signs of allergic conjunctivitis induced by (b) (4)
  - The K-Lens 50 with or without (b) (4) and the positive control ketotifen ophthalmic solution were effective at preventing the signs of allergic conjunctivitis. Mean total redness scores were less for rabbit eyes treated with K-Lens 50 or positive control as compared to contralateral placebo for all assessment time points.
  - K-Lens 50 with (b) (4) demonstrated superior efficacy to both positive control and K-Lens 50 manufactured without (b) (4). The greatest efficacy was noted at 20-minutes post-challenge.

  - K-Lens 50 with [redacted] or without [redacted] in the package solution were effective against [redacted]-induced allergic conjunctivitis in rabbits. While K-Lens 50 with [redacted] was superior to the other active treatments at onset, the performance of K-Lens 50 with or without [redacted] was comparable in terms of duration of effect.

- Study CR-4419: Evaluation of 1-day Acuvue® contact lens with ketotifen fumarate in packing solution: Evaluation of onset and duration of effect in the rabbit
  - Male New Zealand White rabbits (8/treatment) were administered lenses containing 0.005% ketotifen fumarate in the package solution, K-Lens 50 (0.038 mg ketotifen/lens). One of 2 [redacted] (K-Lens 50 [redacted]) or [redacted] (K-Lens 50 [redacted] was also included in the package solution.
    - Group 1: K-Lens 50 [redacted] in one eye and a placebo lens in the other eye.
    - Group 2: K-Lens 50 [redacted] in one eye and a placebo lens in the other eye.
    - Group 3: Positive control, Zaditor (ketotifen fumarate ophthalmic solution, 0.025%), in one eye and placebo (PBS) in the other eye.
  - Fifteen minutes after insertion of the lenses, all rabbits were challenged with 25 µL of 30 mg/mL of [redacted].
  - Following the final ocular examination at 60-minutes post-challenge, lenses were removed.
  - K-Lens 50 [redacted] prevented redness in conjunctival, ciliary and episcleral vessel beds at all post challenge assessment times up to 60-minutes post-challenge. The greatest efficacy was observed 30-minutes post-challenge. K-Lens 50 [redacted] also demonstrated a trend towards preventing chemosis.
  - K-Lens 50 [redacted] and the positive control, Zaditor, were ineffective at preventing vessel bed redness, chemosis, lid edema, tearing or mucus discharge.
  - On Day 7, the same 24 rabbits were again randomized to the 3 treatment groups mentioned above to evaluate the duration of effect.
    - [redacted] 2 hours after insertion of lenses and animals were assessed for ocular signs at 10, 15, 20, 30 and 60-minutes post-challenge.
    - Lenses were removed following the final ocular examination.
    - K-Lens 50 [redacted] was effective at preventing redness in conjunctival, ciliary and episcleral vessel beds with greatest efficacy observed at 20-minutes post-challenge. K-Lens 50 [redacted] also appeared to prevent chemosis at 20 and 30-minutes post-challenge.
    - K-Lens 50 [redacted] was not effective at preventing any of the primary parameters examined which is contrary to the findings in the first study reviewed above. While highly varied mean differences for ocular redness were noted, the reason for this disparity is unknown.

- Zaditor (positive control) also demonstrated efficacy at preventing ciliary, conjunctival and episcleral redness at all post-challenge assessment time points, with greatest efficacy observed at 20-minutes post-challenge. However, Zaditor did not have a preventative effect on chemosis, lid edema, tearing or mucus discharge.
- In conclusion, K-Lens 50 (b) (4) was effective at preventing vessel bed redness and showed a trend toward preventing chemosis in studies to assess onset of action. K-Lens 50 (b) (4) and Zaditor were effective at preventing signs of allergic conjunctivitis in studies to assess duration of action but were not effective in onset of action studies.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Reviewer's note: Ketotifen is extensively metabolized in humans and three distinct metabolites have been detected in human urine. The main metabolite is the N-glucuronide, comprising roughly 50% of urinary drug product, 5 with the N-demethylated nor-ketotifen and the 10-hydroxyl derivative comprising 2% and <1%, respectively.

Study CVV00001-05_05_1136: Assessment of binding of test compound to melanin (ketotifen fumarate)

- (b) (4); GLP
- The study determined the in vitro binding of ketotifen fumarate (0 – 30µM) to synthetic melanin in the presence of (b) (4)
- Ketotifen fumarate did not exhibit high affinity for synthetic melanin at the concentrations tested. Relative to the positive control (chloroquine), ketotifen fumarate was considered to interact weakly with synthetic melanin. The presence of (b) (4) decreased (~3-fold) the low affinity interaction of ketotifen fumarate with melanin.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Six month ocular irritation and toxicity study in the rabbit

Study no.:	07T-44476-02
Study report location:	\\CDSESUB1\evsprod\nda022388\0001\m4\42-stud-rep\423-tox\4236-loc-tol\07t-44476-02\07t-44476-02.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8-17-2007
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	1X K-lens (b) (4) Lot CL005MC 2X K-lens Lot CL005XR

Key Study Findings

- Rabbits administered the K-lens daily for 6 months was not associated with adverse toxicity. The high dose, 2X K-lens, contained 0.038 mg of ketotifen per lens and provides a safety margin of 2-fold over the proposed human dose (0.019 mg/lens)

Methods	
	The contact lenses (1-day Acuvue®) were packaged in 0.0043% ketotifen fumarate (0.019 mg ketotifen per lens) or 0.0086% ketotifen fumarate (0.038 mg ketotifen per lens)
Doses:	Group 1: No treatment Group 2: Placebo lens (Acuvue®) Group 3: Ketotifen ophthalmic solution (Zaditor®) by topical ophthalmic instillation; BID, bilateral Group 4: 1X K-lens (0.019 mg ketotifen/lens); bilateral Group 5: 2X K-lens (0.038 mg ketotifen/lens); bilateral
Frequency of dosing:	Lens replaced daily; daily wear was a minimum 7hours/day. Lens retention was checked hourly during each lens wear day. Lens retention was >99% in all groups treated with the lens.
Formulation/Vehicle:	Clinical formulation including (b) (4) % (b) (4)
Species/Strain:	New Zealand White rabbit
Number/Sex/Group:	6/sex/group
Age:	3.5 – 6 months
Weight:	2.8 – 4.0 kg
Deviation from study protocol:	No deviations were considered to significantly affect study conduct or interpretation of results.

Observations and Results

Mortality

- No deaths of animals or sacrifices prior to schedule were attributed to the test article.

Clinical Signs

- No changes in clinical signs attributed to the test article.

Body Weights

- No changes in body mass or body mass gain attributed to the test article.

Feed Consumption

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy

- Slight conjunctival redness was noted in control and test eyes with similar frequency.
- Neither the K-lens or the Zaditor® treatment resulted in ophthalmic irritation scores higher than untreated controls.

Treatment	Total Scores	Percent of possible Draize score*	Percent of a possible 86,880 conjunctival score
Group 1 (Control – no treatment)	934	0.20	1.1
Group 2 (Control – placebo lens)	2,112	0.44	2.4
Group 3 (Control – ketotifen ophthalmic solution)	2,310	0.49	2.7
Group 4 (Test – 1X)	1,178	0.25	1.4
Group 5 (Test – 2X)	2,034	0.43	2.3

*Possible Draize score for Group 1 is 477,840†. Possible Draize score for Groups 2 through 5 is 475,200†. This difference is due to one extra day of scoring based on termination. Groups 2 through 5 were terminated on Day 180. Group 1 was terminated on Day 181.
†Possible Draize score is calculated by multiplying the number of animals per group (12) by the number of eyes scored (2) by the total possible score each day (110) by the number of days (either 180 or 181).

Hematology

- No changes in hematological parameters attributed to the test article.

Clinical Chemistry

- No changes in clinical chemistry parameters attributed to the test article.

Urinalysis

- No changes in urine chemistry attributed to the test article.

Gross Pathology

- No macroscopic changes attributed to the test article.

Organ Weights

- No changes in organ weights attributed to the test article.

Histopathology

Adequate Battery: Heart, liver, lungs, spleen, thymus, kidneys, adrenal glands, mesenteric lymph nodes, submandibular lymph nodes, testes, ovaries, both eyes and adnexa.

Peer Review: No

Histological Findings

- Spleen
  - Increased hemosiderin (minimal) in red pulp of spleen
    - Females only
      - Group 1 (no treatment): 2/6 females
      - Group 2 (placebo lens): 2/6 females
      - Group 3 (Zaditor®): 6/6 females
      - Group 4 (1x K-lens): 4/6 females
      - Group 5 (2x K-lens): 6/6 females

- Corneoscleral Junction, Conjunctiva, Eyelid
  - Increased inflammatory cell infiltrates (minimal – mild)
    - Observed in corneoscleral junction with similar incidence in groups with contact lens application (Groups 2, 4, and 5)
    - Observed in palpebral conjunctiva with increased incidence in eyes treated with K-lens 1X and 2X (compared to placebo Acuvue® lens)

Dosing Solution Analysis

- Stability of the K-lens test articles was confirmed for 9 months.

7 Genetic Toxicology

The labeling for Zaditor (prior to OTC switch) read:

> *Ketotifen fumarate was determined to be non-mutagenic in a battery of in vitro and in vivo mutagenicity assays including: Ames test, in vitro chromosomal aberration test with V79 Chinese hamster cells, in vivo micronucleus assay in mouse, and mouse dominant lethal test.*

The novel excipient (b) (4) was tested for genotoxicity:

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial reverse mutation assay (b) (4)

Study no.:	08T_25208-04-05-06
Study report location:	\\CDSESUB1\evsprod\nda022388\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\08t-25208-04-05-06\08t-25208-04-05-06.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2-29-2008
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	(b) (4) Lot# PO711091; 100%

Methods

Strains:	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537; *Escherichia coli*: WP2uvrA
Concentrations in definitive study:	0 (vehicle), (b) (4) µg/plate
Basis of concentration selection:	Toxicity at higher concentrations in a dose range finding study
Negative control:	Vehicle (sodium chloride, 0.9%)
Positive control:	TA 98: Benzo[a]pyrene (2.5 µg/plate) +S9 2-nitrofluorene (5.0 µg/plate) – S9 TA 100: 2-aminoanthracene (2.5 µg/plate) +S9 Sodium azide (2.0 µg/plate) – S9 TA1535: 2-aminoanthracene (2.5 µg/plate) +S9 Sodium azide (2.0 µg/plate) – S9 TA1537: 2-aminoanthracene (2.5 µg/plate) +S9 ICR-191 (2.0 µg/plate) – S9 WP2uvrA: 2-aminoanthracene (20 µg/plate) +S9 Methylmethanesulfonate (3250 µg/plate) – S9
Formulation/Vehicle:	Sodium chloride, 0.9%
Incubation & sampling time:	37 °C for 48 to 72 hours prior to counting

Study Validity

- Revertants in the vehicle-control group were within the normal range for all strains.
- The strain-specific positive controls induced at least a 3-fold increase in the number of colonies compared to the vehicle control.

Results

- No increase in the number of revertants was observed at any concentration of (b) (4) in the presence or absence of S9 liver fractions.
- The test compound was considered to be nonmutagenic.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Genotoxicity: *In vitro* chromosomal aberration study in mammalian cells

Study no.:	08T-25208-02-03-07-08
Study report location:	\\CDSESUB1\evsprod\nda022388\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\08t-25208-02-03-07-08\08t-25208-02-03-07-08.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2-29-2008
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	(b) (4) Lot#PO711091; 100% purity

Methods

Cell line:	Chinese hamster ovary cells (CHO)
Concentrations in definitive study:	0 (vehicle), (b) (4) µg/mL
Basis of concentration selection:	Cytostatic toxicity at higher concentrations in dose range finding study
Negative control:	Cell medium
Positive control:	(-) S9: Mitomycin C (0.15 µg/mL) (+)S9: Cyclophosphamide (10 µg/mL)
Formulation/Vehicle:	Cell Medium (McCoy's 5A medium)
Incubation & sampling time:	37°C for 4hr (with or without S9) or 20hr (without S9) prior to collection and counting

Study Validity

- Vehicle control showed a low incidence of chromosomal aberrations consistent with historical control data.
- Positive controls induced significantly high levels of chromosomal aberrations.

Results

- No increase in the number of chromosomal aberrations was observed at any concentration of (b) (4) in CHO cells incubated in the presence or absence of S9 liver fractions.
- The test compound was considered to be non-clastogenic.

8 Carcinogenicity

The labeling for Zaditor® (prior to OTC switch) did not contain any information of the carcinogenic potential of ketotifen.

9 Reproductive and Developmental Toxicology

The labeling for Zaditor (prior to OTC switch) read:

> *Treatment of male rats with oral doses of ketotifen ≥ 10 mg/kg/day orally [6,667 times the maximum recommended human ocular dose of 0.0015 mg/kg/day on a mg/kg basis (MRHOD)] for 70 days prior to mating resulted in mortality and a decrease in fertility. Treatment with ketotifen did not impair fertility in female rats receiving up to 50 mg/kg/day of ketotifen orally (33,333 times the MRHOD) for 15 days prior to mating.*
>
> *Pregnancy Category C*
> *Oral treatment of pregnant rabbits during organogenesis with 45 mg/kg/day of ketotifen (30,000 times the MRHOD) resulted in an increased incidence of retarded ossification of the sternebrae. However, no effects were observed in rabbits treated with up to 15 mg/kg/day (10,000 times the MRHOD). Similar treatment of rats during organogenesis with 100 mg/kg/day of ketotifen (66,667 times the MRHOD) did not reveal any biologically relevant effects.*
>
> *Oral treatment of pregnant rats (up to100 mg/kg/day or 66,667 times the MRHOD) and rabbits (up to 45 mg/kg/day or 30,000 times the MRHOD) during organogenesis did not result in any biologically relevant embryofetal toxicity. In the offspring of the rats that received ketotifen orally from day 15 of pregnancy to day 21 post partum at 50 mg/kg/day (33,333 times the MRHOD), a maternally toxic treatment protocol, the incidence of postnatal mortality was slightly increased, and body weight gain during the first four days post partum was slightly decreased.*
>
> *Nursing Mothers*
> *Ketotifen fumarate has been identified in breast milk in rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when ketotifen fumarate is administered to a nursing mother.*

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/s/

ERIN M RUHLAND
12/27/2021 12:42:03 PM

LORI E KOTCH
12/27/2021 04:13:56 PM