CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210565Orig1s000

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:	210565
Supporting document/s:	SD 8 (labeling/package insert draft, sent 1/05/2018)
Applicant's letter date:	October 24, 2017
CDER stamp date:	October 24, 2017
Product:	INVELTYS (loteprednol etabonate ophthalmic suspension), 1%
Indication:	Treatment of post-operative inflammation and pain following ocular surgery
Applicant:	Kala Pharmaceuticals, Inc. (Kala) Waltham, Massachusetts 02453, USA
Review Division:	Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), HFD-590
Reviewer:	Andrew J. McDougal, PhD, DABT, DTOP
Supervisor/Team Leader:	Lori E. Kotch, PhD, DABT, DTOP
Division Director:	Renata Albrecht, MD, DTOP
Project Manager:	Dheera Semidey, Pharm.D.

Template Version: September 1, 2010

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Except as specifically identified below, Kala Pharmaceuticals, Inc. claims ownership of all data and information necessary for approval of NDA 210565, or are data for which Kala Pharmaceuticals, Inc. has obtained a written right of reference.
Any information or data necessary for approval of NDA 210565 that Kala Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and were not relied upon for approval of NDA 210565.

Reference ID: 4300881

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1 Executive Summary

1.1 Introduction

- The name of the Applicant is Kala Pharmaceuticals, Inc. (Kala Pharmaceuticals; Kala). On October 24, 2017, Kala submitted NDA 210565 in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act for INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%, seeking approval for the indication of treatment of post-operative inflammation and pain following ocular surgery.
- The NDA relies on FDA's finding of safety and efficacy for Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%, approved under NDA 020-583 (020583, 20583).
- The drug product was developed under Kala's active IND 117192, using the code name KPI-121 1%.
- The nonclinical Pharmacology/Toxicology (P/T) review identified no new safety concerns for INVELTYS™ (Inveltys). P/T recommends approval of the NDA.
- The NDA file is available internally via: \\CDSESUB1\evsprod\NDA210565\210565.enx

1.2 Brief Discussion of Nonclinical Findings

- Loteprednol etabonate (LE) is a corticosteroid ester initially approved in 1998 (Bausch & Lomb's NDA 20-583 for Lotemax®).
- NDA 210565 was submitted under the 505(b)(2) pathway, listing Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%, approved under NDA 020-583.
- Inveltys is 1% loteprednol etabonate, indicated for twice daily (BID) dosing of one or two (b) (4) drops per dose. For comparison, the listed drug (NDA 20583's Lotemax®) is 0.5% loteprednol etabonate, indicated for dosing four times daily (QID), of one or two drops per dose.

1.3 Labeling Recommendations

- Kala submitted draft labeling; the annotations for their nonclinical sections refer to the 2016 labeling for Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%.[1] Kala's draft attempted to update language to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

[1] For NDA 20583, the 2016 labeling appears on an FDA website: https://www.accessdata.fda.gov/spl/data/ae27f407-c1da-4141-8281-2c89ef9ec1fa/ae27f407-c1da-4141-8281-2c89ef9ec1fa.xml . The most recent labeling reviewed by DTOP P/T is the original NDA's labeling (1998), which appears on the Drugs@FDA website: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20583lbl.pdf

Reference ID: 4300881

  - Notably, Bausch and Lomb is the Applicant for NDA 20583 (Lotemax®), and they present labeling on their website revised in 2016. However, DTOP did not review the 2016 labeling.
- Bausch and Lomb has not updated the labeling for NDA 20583 (the listed drug) to comply with the Pregnancy and Lactation Labeling Rule (PLLR) for Lotemax (loteprednol etabonate ophthalmic suspension/drops) 0.5%.
- For NDA 210565, the strength is 1%. The calculations in this review are based on dosing one eye, 2 drops/dose, 2 doses per day.
- Table 1 below has P/T's recommendations for labeling. Table 2 tracks changes from the previous P/T recommendations (McDougal, 7/19/2018, NDA 210565)

Table 1: P/T recommended language

Applicant's proposed text	Reviewer's recommendations
	(b) (4)

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(b) (4)

13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or	[*no change*]

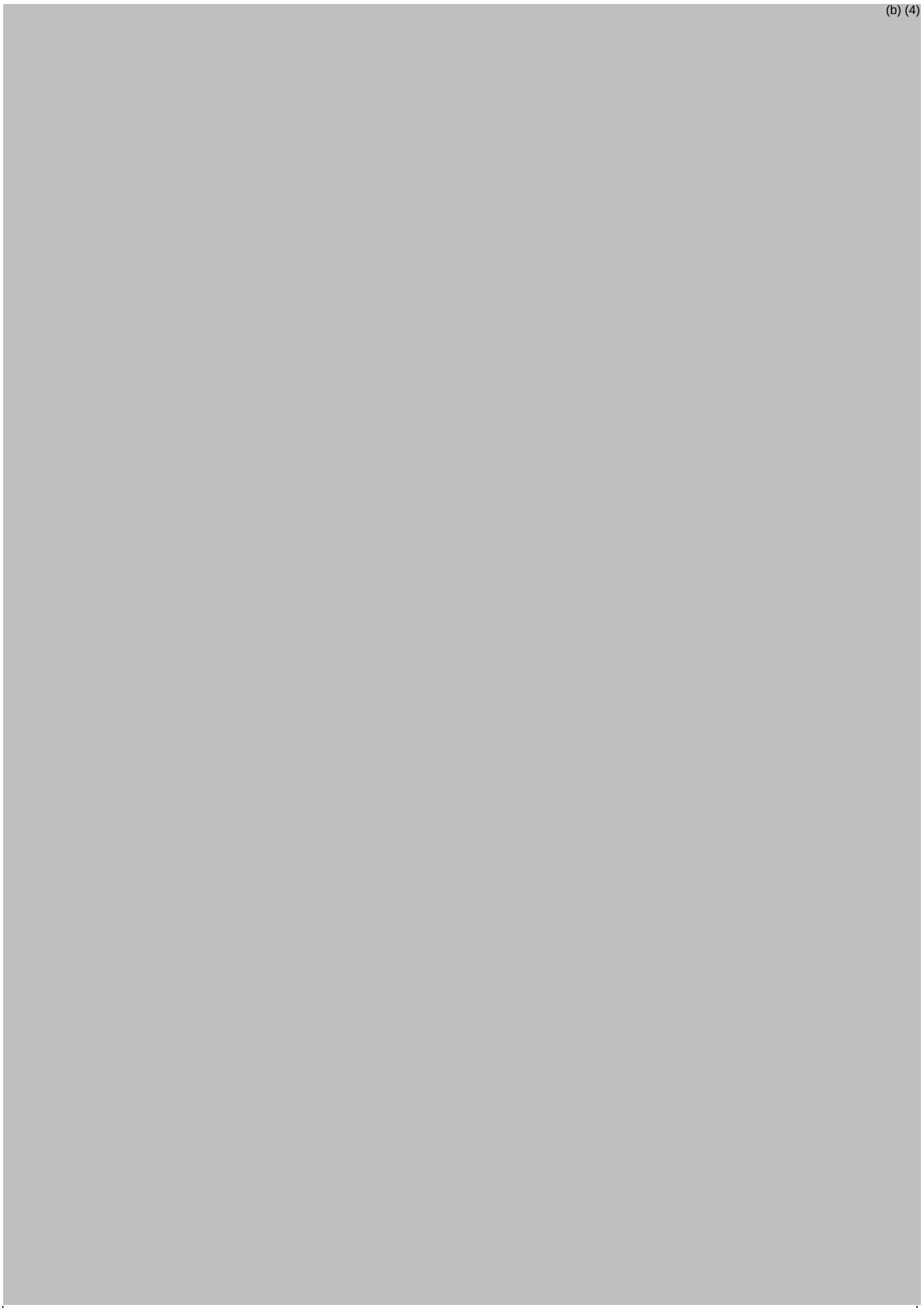
in vivo in the single dose mouse micronucleus assay.	
(b) (4)	*[Section intentionally left blank*]

Table 2: P/T recommended labeling, with changes tracked from the previous review (McDougal, 7/19/2018, NDA 210565)

Dark blue = previously recommended new language
Strike through = language removed from the previously recommended new language
Bold purple = new-in-this review language, to address PLLR and 505(b)(2) questions.

Applicant's proposed text	**New changes to the language previously proposed (7/19/2018) tracked**
USE IN SPECIFIC POPULATIONS **8.1 Pregnancy**	*[keep heading]*
(b) (4)	

(b) (4)



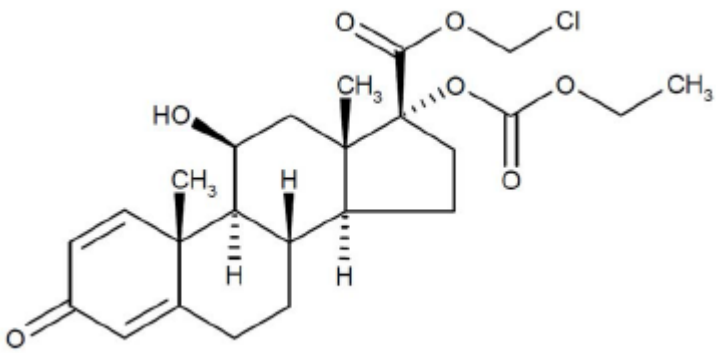
8.2 Lactation	**8.2 Lactation**

Reference ID: 4300881

(b) (4)	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay.	[*no change*]
(b) (4)	*[Section intentionally left blank*]

2 Drug Information

CAS Registry Numbers:	• 82034-46-6 (for loteprednol etabonate) • (b) (4)
Generic Name	Loteprednol etabonate
Code Name	KPI-121
Chemical name	Chloromethyl 17α-[(ethoxycarbonyl)oxy]- 11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate
Molecular formula	$C_{24}H_{31}ClO_7$
Molecular Weight	466.96 grams per mole
Structure	**Figure 1: structure of loteprednol etabonate**

	 [From NDA module 1.14 Labeling]
Pharmacological class	corticosteroid

3 Previous Review Referenced

This review references the previous P/T review for NDA 210565 (McDougal, 7/19/2018).

9 Reproductive and Developmental Toxicology

The Applicant did not conduct reproductive toxicology, developmental toxicology, or fertility studies. The Applicant is relying on the Agency's finding of safety and effectiveness for Lotemax® (NDA 20583), as described in published labeling. The labeling for Lotemax® (NDA 20583) is not yet PLLR-compliant.

This reviewer's recommended labeling for Inveltys (above in this review) is PLLR-compliant. The Applicant's proposed labeling is based on approved labeling for NDA 20583, and is factually inaccurate in the following:

(b) (4)

11 Integrated Summary and Safety Evaluation

- Kala submitted this NDA for Inveltys is submitted under the 505(b)(2) pathway, listing NDA 20583 for Lotemax (Loteprednol etabonate 0.5%) ophthalmic

suspension/drops. Drugs@FDA has the original 1998 labeling[2]. Additionally, the Applicant submitted 2016 labeling[3], which is published at Accessdata.fda.gov[4] but which was not reviewed by DTOP prior to publication.

- For both approved Lotemax, and for Inveltys, the clinical indication is "treatment of postoperative inflammation and pain following ocular surgery".
- P/T completed a review of the NDA (McDougal, 7/19/2018, NDA 210565). DTOP management requested labeling recommendations based only on the current labeling for the listed drug (Lotexmax' NDA 20583 current labeling) and information submitted by the Applicant in their NDA 210565.
    - This labeling review was drafted in response, using the current labeling for NDA 20583. No information from previous P/T reviews, the study reports, or other sources was used directly.
    - Reviewer note: the dose margins for the rat EFD study are based on the rat doses reported in labeling for NDA 20583, and Kala's information regarding their drop size, dosage and administration.

[2] NDA 20583. Labeling dated 3/09/1998, accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20583lbl.pdf
[3] NDA module 1.14.3 Listed drug labeling, \\cdsesub1\evsprod\nda210565\0001\m1\us\114-label\1143-list-drug-label\lotemax-pi-2016.pdf
[4] Labeling for "LOTEMAX- loteprednol etabonate suspension/ drops Bausch & Lomb Incorporated" revised 9/2016, accessed via: https://www.accessdata.fda.gov/spl/data/ae27f407-c1da-4141-8281-2c89ef9ec1fa/ae27f407-c1da-4141-8281-2c89ef9ec1fa.xml

Reference ID: 4300881

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW J MCDOUGAL
08/01/2018

LORI E KOTCH
08/01/2018

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:	210565
Supporting document/s:	SD 1 (original NDA, sent 10/24/2017) SD 6 (labeling/package insert draft, sent 12/21/2017) SD 8 (labeling/package insert draft, sent 1/05/2018)
Applicant's letter date:	October 24, 2017
CDER stamp date:	October 24, 2017
Product:	INVELTYS (loteprednol etabonate ophthalmic suspension), 1%
Indication:	Treatment of post-operative inflammation and pain following ocular surgery
Applicant:	Kala Pharmaceuticals, Inc. (Kala) Waltham, Massachusetts 02453, USA
Review Division:	Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), HFD-590
Reviewer:	Andrew J. McDougal, PhD, DABT, DTOP
Supervisor/Team Leader:	Lori E. Kotch, PhD, DABT, DTOP
Division Director:	Renata Albrecht, MD, DTOP
Project Manager:	Dheera Semidey, Pharm.D.

Template Version: September 1, 2010

Reference ID: 4293985

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1 Executive Summary

1.1 Introduction

- The name of the Applicant is Kala Pharmaceuticals, Inc. (Kala Pharmaceuticals; Kala). On October 24, 2017, Kala submitted NDA 210565 in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act for INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%, seeking approval for the indication of treatment of post-operative inflammation and pain following ocular surgery.
- The NDA relies on FDA's finding of safety and efficacy for Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%, approved under NDA 020-583 (020583, 20583).
- The drug product was developed under Kala's active IND 117192, using the code name KPI-121 1%.
- The nonclinical Pharmacology/Toxicology (P/T) review identified no new safety concerns for INVELTYS™ (Inveltys). P/T recommends approval of the NDA.
- The NDA file is available internally via: \\CDSESUB1\evsprod\NDA210565\210565.enx

1.2 Brief Discussion of Nonclinical Findings

- Loteprednol etabonate (LE) is a corticosteroid ester initially approved in 1998 (Bausch & Lomb's NDA 20-583 for Lotemax®).
- Kala has proposed to describe their product in labeling (section 11 Description) as

  "INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1% contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use.

  (b) (4)

- NDA 210565 was submitted under the 505(b)(2) pathway, listing Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%, approved under NDA 020-583. From a P/T perspective, the finding of safety for Inveltys is based on the Applicant's submitted data, and the listed drug (Lotemax®).
  - The Applicant provided published literature in support of conclusions reached regarding the nonclinical data. From a nonclinical Pharmacology/Toxicology (P/T) perspective, none of the submitted literature is essential to demonstrate safety.
  - One paper submitted by the Applicant, Schopf et al. 2014, is a comparative ocular PK study in rabbits comparing Lotemax® to an early formulation of KPI-121 (4% loteprednol etabonate).

        - This paper uses the trade name Lotemax® (i.e. referring to NDA 20583's drug product), and also uses the code name LE-MPP 0.4% (a code name of the Applicant for KPI-121).
        - The results of this paper provide further support for the PK bridge between Lotemax and Inveltys.
    - Several of the published literature represent scientific common knowledge for the chemical class (corticosteroids).
    - Review verified that the other published literature either used the trade name Lotemax®, or did not mention any commercial/trade names.
- Inveltys is 1% loteprednol etabonate, indicated for twice daily (BID) dosing of one or two (b) (4) drops per dose. For comparison, the listed drug (NDA 20583's Lotemax®) is 0.5% loteprednol etabonate, indicated for dosing four times daily (QID), of one or two drops per dose.
- The Applicant submitted a 28-day ocular toxicology study in rabbits (report # 8286658), testing the clinical dose (KPI-121 1%). From a nonclinical perspective, treatment was well-tolerated and the study establishes ocular safety and systemic safety. Consistent with expected pharmacology, treatment-related effects were observed:
    - eyelid decreased anagen hair follicles
    - weight loss, adrenal cortex atrophy
    - Decreased circulating lymphocytes, correlating with decreased spleen and thymus weight

1.3 Recommendations

1.3.1 Approvability

P/T recommends approval of NDA 210565.

1.3.2 Additional Nonclinical Recommendations

P/T requirements and recommendations have been fulfilled, for the clinical indication described in the original NDA 210565 submission. P/T has no recommendations for further testing.

1.3.3 Labeling

- Kala submitted draft labeling; the annotations for their nonclinical sections refer to the 2016 labeling for Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%.[1] Kala's draft attempted to update language to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

[1] For NDA 20583, the 2016 labeling appears on an FDA website: https://www.accessdata.fda.gov/spl/data/ae27f407-c1da-4141-8281-2c89ef9ec1fa/ae27f407-c1da-4141-8281-2c89ef9ec1fa.xml . The most recent labeling reviewed by DTOP P/T is the original NDA's labeling (1998), which appears on the Drugs@FDA website: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20583lbl.pdf

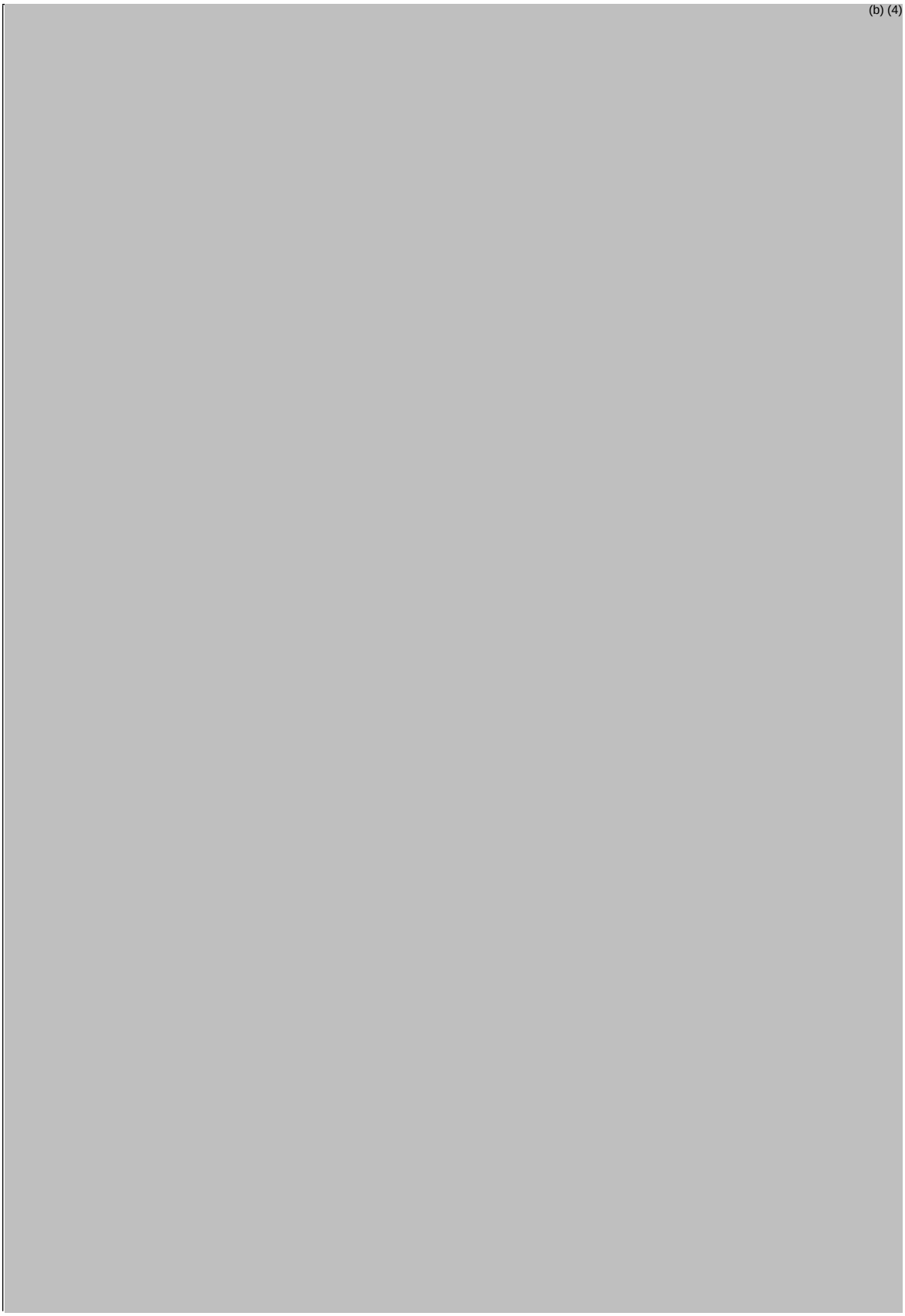
Reference ID: 4293985

  - Notably, Bausch and Lomb is the Applicant for NDA 20583 (Lotemax®), and they present labeling on their website revised in 2016. However, DTOP did not review the 2016 labeling.
- Bausch and Lomb has not updated the labeling for NDA 20583 (the listed drug) to comply with the Pregnancy and Lactation Labeling Rule (PLLR) for Lotemax (loteprednol etabonate ophthalmic suspension/drops) 0.5%. However, Bausch and Lomb has submitted PLLR labeling for NDA 202872 for Lotemax (loteprednol etabonate ophthalmic gel) 0.5%. Both NDAs rely on the same nonclinical study reports for fertility, developmental and reproductive toxicology. The P/T review for PLLR (McDougal, 3/20/2018, NDA 202872) is complete, and the same language should be used to describe the same nonclinical data (dose margins adjusted as appropriate).
  - Although Kala did not explicitly list NDA 202872, all of the loteprednol labeling rely on these same studies, and will be required to have the same PLLR language (adjusted for differences in the dosage and administration).
  - Anticipating approval of the PLLR language for loteprednol etabonate, DTOP directed P/T to use the same PLLR language for Inveltys, as is/will be approved for NDA 202872.
  - For NDA 202872, the strength was 0.5%. The calculations were based on dosing one eye, 2 drops/dose, 4 doses per day, (b) (4)
  - For NDA 210565, the strength is 1%. The calculations in this review are based on dosing one eye, 2 drops/dose, 2 doses per day.

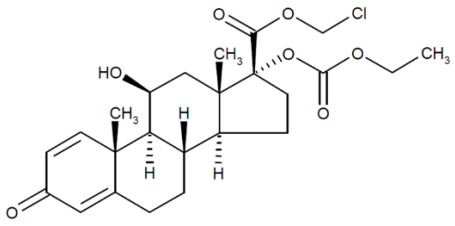
Applicant's proposed text	Reviewer's recommendations
USE IN SPECIFIC POPULATIONS **8.1 Pregnancy**	*[keep heading]*
(b) (4)	

Reference ID: 4293985

(b) (4)



(b) (4)

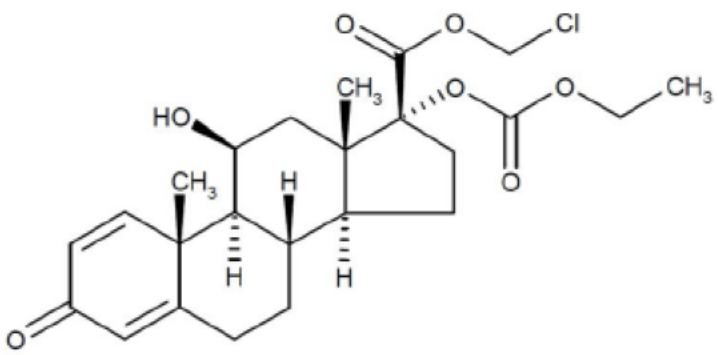
11 Description	11 Description
INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1% contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. (b) (4) 	**Loteprednol etabonate is a corticosteroid. Its chemical name is chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate. Its molecular formula is $C_{24}H_{31}ClO_7$ and its chemical structure is:** … **INVELTYS™** (loteprednol etabonate ophthalmic suspension) 1% contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use.

$C_{24}H_{31}ClO_7$ Mol. Wt. 467.0 Chemical Name: chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3oxoandrosta-1,4-diene-17β-carboxylate	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay.	[*no change*]
[redacted] (b) (4)	

2 Drug Information

2.1 Drug

CAS Registry Numbers:	• 82034-46-6 (for loteprednol etabonate) [redacted] (b) (4)
Generic Name	Loteprednol etabonate
Code Name	KPI-121
Chemical name	Chloromethyl 17α-[(ethoxycarbonyl)oxy]- 11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate
Molecular formula	$C_{24}H_{31}ClO_7$
Molecular Weight	466.96 grams per mole
Structure	**Figure 1: structure of loteprednol etabonate**

	 [From NDA module 1.14 Labeling]
Pharmacological class	corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

- The Applicant's referenced seven drug master files on their FDA form 356h: DMF # (b) (4), DMF # (b) (4), DMF # (b) (4), DMF # (b) (4), DMF # (b) (4), DMF # (b) (4), DMF # (b) (4). Statements of right of reference were provided for each DMF in NDA module 1.4 (References).
  - P/T defers to the Quality Review team, regarding review of the DMFs and adequacy of the references.
  - Notably, the holder of DMF (b) (4); the subject of the DMF is the manufacture of the loteprednol etabonate drug substance.
- The Applicant's NDA 210565 referenced their active IND 117192, under which the drug was developed.
- The Applicant's form 356h cross references 5 NDAs: the listed drug NDA (NDA 20-583), and four additional NDAs listed as "related": NDA 20-803, NDA 20-841, NDA 200-738, NDA 202-872.

Table 1: FDA-approved NDAs for loteprednol etabonate

NDA #	Applicant	Trade name	Dose of loteprednol etabonate	Route	Marketing status
20583	Bausch & Lomb	Lotemax	0.5%	Ophthalmic suspension/drops	Prescription
20803	Bausch & Lomb	Alrex	0.2%	Ophthalmic suspension /drops	Prescription
20841	Bausch & Lomb	Lotemax	0.5%	Ophthalmic suspension/drops	Prescription

50804	Bausch & Lomb	Zylet	0.5% (+ 0.3% tobramycin)	Ophthalmic suspension/drops	Prescription
200738	Pharmos	Lotemax	0.5%	Ophthalmic ointment	Discontinued
202872	Bausch & Lomb	Lotemax	0.5%	Ophthalmic gel	Prescription

2.3 Drug Formulation

From the NDA's Description and Composition of the Drug Product (NDA module 3.2.P.1)

- "KPI-121 1% is a sterile aqueous (b) (4) suspension of loteprednol etabonate (LE) for topical ophthalmic use. Each milliliter of KPI-121 1% contains 10 mg LE as the active ingredient. Inactive ingredients are glycerin, sodium citrate dihydrate, poloxamer 407, sodium chloride, edetate disodium dihydrate, citric acid, and water for injection. Benzalkonium chloride (0.01% w/v) is added as preservative. KPI-121 1% is essentially (b) (4)
- KPI-121 1% is supplied in a dropper bottle of 5 ml nominal capacity. The bottle has a "controlled-drop linear low-density polyethylene tip" and delivers approximately (b) (4) of KPI-121 1% per drop."
  - The commercial bottle contains 2.8 ml of KPI-121 1%
  - The physician sample contains 1.2 ml of KPI-121 1%.

Table 2: Inveltys (KPI-121) 1% drug product formulation

Ingredient	Quality Standard	Function	Amount (mg) in each mL of KPI-121 1%	Concentration (%w/v) in KPI-121
Loteprednol etabonate	DMF # (b) (4)	Active Pharmaceutical Ingredient	10	1.0
Glycerin	USP-NF	(b) (4)		
Sodium citrate, dihydrate	USP-NF			
Poloxamer 407	USP-NF			
Sodium chloride	USP-NF			
Edetate disodium, dihydrate	USP-NF			
Citric acid, (b) (4)	USP-NF			

Benzalkonium chloride	USP-NF	Preservative	0.1	0.01
Water for injection	USP-NF	[redacted] (b) (4)		

USP-NF: United States Pharmacopeia – National Formulary.
[redacted] (b) (4)

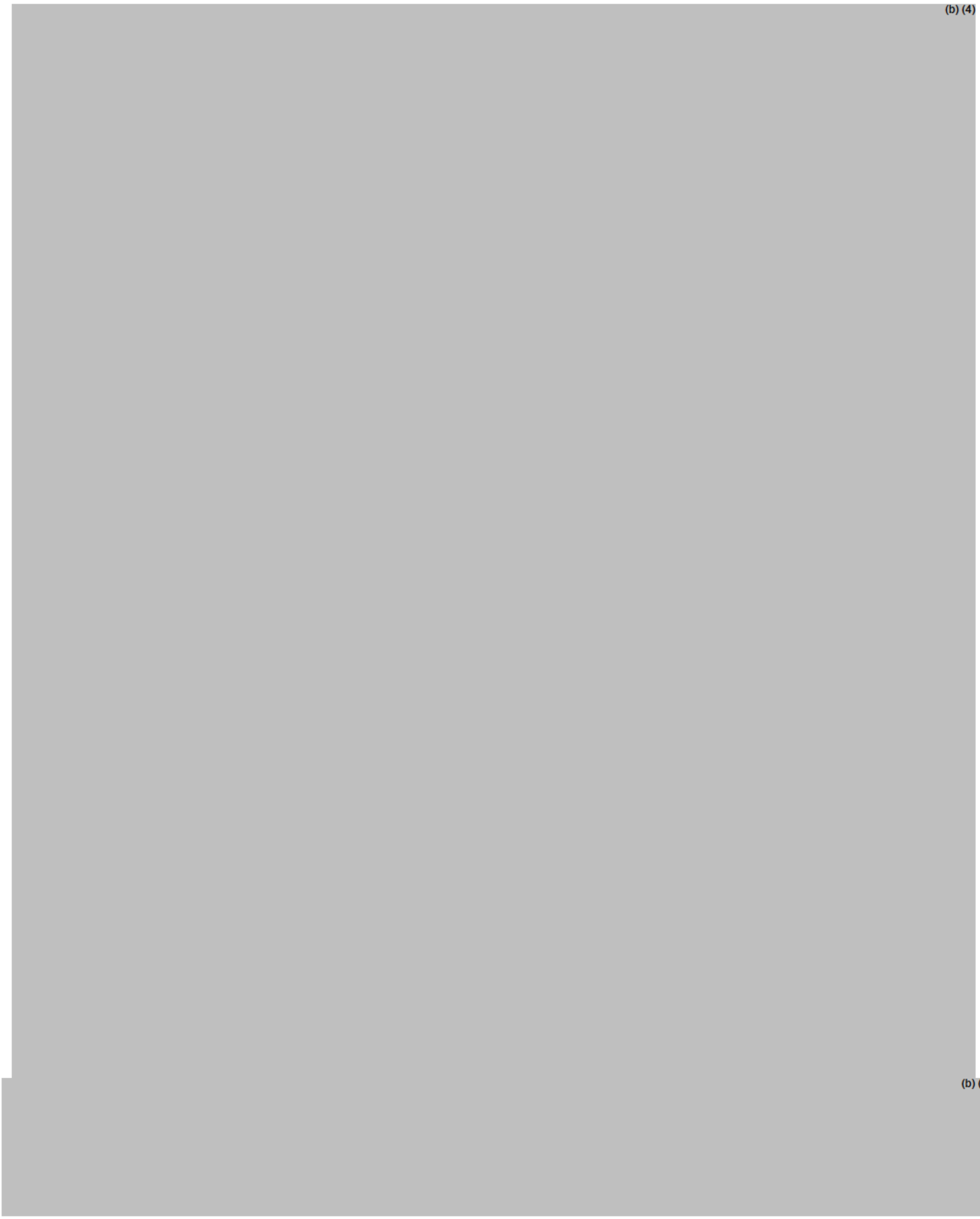
2.4 Comments on Novel Excipients

- As noted in the table above, the excipients used in KPI-121 1% are compendial.
- As noted in approved labeling for the listed drug (NDA 20583), Lotemax' excipients are "glycerin, [redacted] (b) (4) edetate disodium [redacted] (b) (4) with 0.01% benzalkonium chloride preservative.
- The excipients were qualified by the rabbit 28-day ocular toxicology study (report # 8286658).
- Based on the CDER Inactive Ingredient Search for Approved Drug Products[2],[3]:
  - This use of [redacted] (b) (4) (b) (4) NDA 50810 for Azasite (azithromycin)[4], [redacted] (b) (4) NDA 22308 for Besivance (besifloxacin hydrochloride)[5].
  - This use of glycerin [redacted] (b) (4) ANDA 87681 for Paracain (proparacaine hydrochloride)[6].

2.5 Comments on Impurities/Degradants of Concern

- The impurity profile for the Inveltys drug product is not concerning from a P/T perspective.
  - The NDA's Control of Drug Product (NDA module 3.2.P.5) notes that [redacted] (b) (4) The amount detected was [redacted] (b) (4) The presence of [redacted] (b) (4) is not concerning.

[2] IIS internet link (available to the public) accessed via: https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
[3] ISS intranet link accessed via: http://intranetapps.dev.fda.gov/scripts/iig/index.cfm
[4] For NDA 50810/S-012, the 2012 labeling was accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050810s012lbl.pdf
[5] For NDA 22308/S-013, the 2018 labeling was accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022308s013lbl.pdf
[6] For ANDA 87681, approval was granted in 1982. Labeling does not appear at Drugs@FDA.


(b) (4)
(b) (4)

- Under the Drug Product Justification of Specifications (NDA module 3.2.P.5.6), the Applicant submitted two computational structure-activity relationship (SAR) reports evaluating the structure of the (b) (4) impurity for activity in the Ames genotoxicity assay. The predictions were not concerning.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Per the Applicant's draft labeling (NDA module 1.14 Labeling):

- Indications and usage: "INVELTYS™ is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery."
- Dosage forms and strengths: "INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1% contains 10 mg/mL of loteprednol etabonate, as a sterile preserved (b) (4) ophthalmic suspension."
- Contraindications: "INVELTYS™, (b) (4), is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures."

2.7 Regulatory Background

- The drug product was developed under Kala's IND 117192.
- NDA 210565 was submitted on 10/24/2017. No P/T information requests have been drafted for the NDA.

3 Studies Submitted

3.1 Studies Reviewed

Table 3: List of submitted nonclinical studies

Laboratory Report #	Study Title	[a]Kala summary report #
8286656	Validation of a Method for the Determination of KPI-121 in Rabbit Plasma by HPLC with MS/MS Detection	[none]

Reference ID: 4293985

2012-206	Pharmacokinetics of Loteprednol Etabonate (LE) in Aqueous Humor Following Topical Dosing with Formulations of Various Concentrations	KPI-121-T001
2013-030	Pharmacokinetics of Loteprednol Etabonate (LE) in Ocular Tissues Following Topical Dosing with Either One of Two LE Test Formulations	KPI-121-T003
2013-068	Pharmacokinetics of Loteprednol Etabonate (LE) in Ocular Tissues Following Topical Dosing with LE Test Formulations	KPI-121-T002
2013-150	Pharmacokinetics of Loteprednol (1%) of Various Particle Size Administered Topically in a MPP Formulation	KPI-121-T022
8286658	28-Day Ocular Instillation Toxicity and Toxicokinetic Study with KPI-121 in Rabbits	KPI-121-T005

[a] Aside from the analytical validation report (# 8286656), Kala provided a short summary report separate from each laboratory report. These summaries were fully reviewed, toward understanding the Applicant's interpretation of the study results. For the IND, Kala's reports were included in the same pdf file as the laboratory report. For the NDA, Kala provided their summary reports in separate pdf files from the laboratory report.

Table 4: Computational structure activity relationship (SAR) reports for the (b) (4) impurity

(b) (4)

3.2 Studies Not Reviewed

- All submitted study reports were fully reviewed.

- In addition to the study reports submitted, the Applicant provided three publications, describing ocular PK for Lotemax (0.5% suspension or 0.5% gel) [14], [15] and KPI-121 4%[16].
    - Because the commercial drug product is KPI-121 1%, review of these papers is not fully documented in this review.
- The Applicant's Nonclinical Overview (NDA module 2.4) cited literature references to demonstrate the safety of KPI-121. The literature was provided to the NDA (module 4.3), but was not fully reviewed.

3.4 Previous Reviews Referenced

- As noted above, the Applicant's NDA references their active IND 117192 for loteprednol etabonate. This P/T review references:
    - The minutes of the pre-IND meeting held on 4/03/2013 (Puglisi, 4/26/2013, IND 11792)
    - The three P/T reviews of the IND (McDougal, 1/23/2014; McDougal 7/28/2017; McDougal 8/30/2017; IND 117192).
- This NDA lists NDA 020583 (Lotemax). NDA 20583 was originally submitted by Pharmos; the current Applicant is Bausch and Lomb. For completeness-of-record, the public availability of a redacted version of the P/T review for the original NDA 20583 submission is noted[17]. The NDA 20583 PT review was not necessary to support the safety of KPI-121.
- As explained above, the P/T review (McDougal, 3/20/2018) and the DTOP Action Summary Review for NDA 202872/Supplement 2 (pending) are referenced.
    - At the DTOP internal filing meeting and mid-cycle meeting for NDA 210565, DTOP made the determination (Chambers/McDougal, 12/15/2017 and 3/13/2018, respectively) to use the current PLLR language for loteprednol in Inveltys's labeling, to inform physicians and patients with the most up-to-date labeling language available.

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[14] Druzgala P, Wu WM, Bodor N. 1991. Ocular absorption and distribution of loteprednol etabonate, a soft steroid, in rabbit eyes. Curr Eye Res. 10:933-937.
[15] Glogowski S, Lowe E, Siou-Mermet R, Ong T, Richardson M. 2014. Prolonged exposure to loteprednol etabonate in human tear fluid and rabbit ocular tissues following topical ocular administration of Lotemax gel, 0.5%. J Ocul Pharmacol Ther. 30:66-73.
[16] Schopf L, Enlow E, Popov A, Bourassa J, Chen H. 2014. Ocular pharmacokinetics of a novel loteprednol etabonate 0.4% ophthalmic formulation. Ophthalmol Ther. 3:63-72.
[17] NDA 20583. P/T review by Dr. David A. Shriver, available as two parts via: https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20583_LOTEMAX_pharmr_P1.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20583_LOTEMAX_pharmr_P2.pdf

4 Pharmacology

4.1 Primary Pharmacology

The Applicant did not submit primary pharmacology, secondary pharmacology, or safety pharmacology studies with KPI-121.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The Applicant submitted on validation report (for the detection of loteprednol etabonate in rabbit plasma) and four rabbit PK studies (topical ocular dosing). Additionally, the Applicant provided one paper testing KPI-121 4% (Schopf et al. 2014).

Report title	**Validation of a Method for the Determination of KPI-121 in Rabbit Plasma by HPLC with MS/MS Detection**
Report #	8286656
File location	NDA module 4.2.2 Pharmacokinetics: Analytical Methods and Validation Reports: \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4221-analyt-met-val\8286656\8286656.pdf
Report date and status:	• Study initiated July 22, 2013 • Final validation report, dated 11/11/2013. • Not GLP. Quality assurance was performed.
Study laboratory:	(b) (4)
Summary	• Detection was validated for the range 0.100 to 200 ng/mL for detection of loteprednol etabonate in rabbit plasma samples of at least 0.100 ml. • The detection method was liquid-liquid extraction / LC-MS/MS • The test article was loteprednol etabonate, batch # PR121380 (purity 99.83%)

Title	**Pharmacokinetics of Loteprednol Etabonate (LE) in Ocular Tissues Following Topical Dosing with LE Test Formulations**
Report #s	• 2013-068 (study laboratory #) • KPI_121-T-002 (Applicant's code #)
Key findings	• The purpose of this study was to compare four different formulations against Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%

Reference ID: 4293985

		○ None of the formulations tested are the same as the clinical formulation • Groups of 3 male NZW rabbits/dose/time point were sacrificed at 6 time points (from 5 minutes to 6 hours post-dose). • PK for loteprednol in aqueous humor, cornea, retina, and plasma were measured. Distribution: cornea > aqueous humor > retina > plasma
		• As would be expected for comparing Lotemax (0.5% loteprednol etabonate) to 1% loteprednol etabonate (in formulations close to the commercial clinical drug product) with a single dose, concentrations were slightly higher for the KPI-121 1% formulations, compared to Lotemax • This reviewer concludes that the similarity in concentrations across the tissues measured supports using the safety data for Lotemax® (as inferred from approval of NDA 20583) in support of Inveltys.
Report details	Report dates and status	• Study initiated April 1, 2013 • Final report signed June 19, 2013 • Not GLP
	Study laboratory	(b) (4)
	Report location	NDA module 4.2.2.2 Pharmacokinetics: absorption: \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2013-068\2013-068.pdf and \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2013-068\kpi-121-t-002.pdf
Methods	Species	A total of 36 male New Zealand White rabbits, 6 months old at time of dosing, weight range 2.81 to 3.58 kg
	Dose groups	4 dose groups: • Group 1: Lotemax® (0.5% loteprednol etabonate ophthalmic suspension) • Group 2: loteprednol 1% (b) (4) • Group 3: loteprednol 1% (b) (4) • Group 4: loteprednol 1% (b) (4) *Reviewer note*: The Applicant's summaries (NDA module 2.6.4 Pharmacokinetics Written Summary and 2.6.5 Pharmacokinetics Tabulated Summary) compare Lotemax® with Group 2 only.
	Dosing	Single 50 µl topical ocular dose in both eyes
	Sample collection	• Time points: ○ For Lotemax® and group 2: 5, 15, 30 minutes; 1, 3, and 6 hours post-dose [PK parameters calculated]

Reference ID: 4293985

<table>
<tr><td></td><td></td><td>

For Groups 3 and 4, time points were 15 minutes, 30 minutes, and 1 hour [PK parameters not calculated]

• Blood was collected (for plasma) prior to euthanasia. Aqueous humor, cornea, and retina (center punch) were collected for measurement of loteprednol etabonate.
</td></tr>
<tr><td></td><td>Test articles:</td><td>
• Commercial Lotemax® was used.
• For the KPI-121 groups, the formulation was close to the clinical formulation: 1% loteprednol etabonate, (b) (4)% poloxamer 407, (b) (4)% sodium chloride, (b) (4)% EDTA, and 0.01% BAC.
• The clinical drug product is % loteprednol etabonate, (b) (4)% Poloxamer 407, (b) (4)% glycerin, (b) (4)% sodium citrate, (b) (4)% sodium chloride, and 0.01% BAC.
• Therefore, the test articles differ from the final clinical drug product in glycerin (b) (4)% versus (b) (4)%), sodium citrate ((b) (4) versus (b) (4)%) and sodium chloride ((b) (4)% versus (b) (4)%).
</td></tr>
<tr><td>PK Results:</td><td colspan="2">
• As noted above, the authors and Applicant compared Lotemax® to group 2 (b) (4)
○ The NDA's manufacturing summary (NDA module 3.2.P.3) reports that the drug product is (b) (4) but no mention of " (b) (4) was identified.
○ This reviewer infers that the (b) (4)
• The lower limit of quantitation (LLOQ) was 0.0200 ng/ml for fluid (aqueous humor and plasma) and 0.0200 ng/g for tissue (cornea and retina)

Table 5: Loteprednol etabonate TK in rabbits following a single topical ocular dose of Lotemax (0.5%) or a formulation of 1% loteprednol etabonate similar to the clinical drug product (report # 2013-068)
<table>
<tr><th>Tissue</th><th>Test article</th><th>$t_{1/2}$ (h)</th><th>T_{max} (hr)</th><th>C_{max} (ng/ml or ng/g)</th><th>AUC_{0-6hr} (ng*h/ml or ng*hr/g)</th></tr>
<tr><td rowspan="2">Aqueous humor</td><td>Lotemax 0.5%</td><td>0.962</td><td>0.50</td><td>6.88</td><td>11.3</td></tr>
<tr><td>KPI-121 1%</td><td>0.874</td><td>0.50</td><td>25.8</td><td>40.7</td></tr>
<tr><td rowspan="2">Cornea</td><td>Lotema 0.5%</td><td>1 87</td><td>0 083</td><td>632</td><td>695</td></tr>
<tr><td>KPI-121 1%</td><td>1.39</td><td>0.083</td><td>1730</td><td>1810</td></tr>
<tr><td rowspan="2">Retina</td><td>Lotemax 0.5%</td><td>2.45</td><td>0.25</td><td>3.75</td><td>7.33</td></tr>
<tr><td>KPI-121 1%</td><td>2.59</td><td>0.50</td><td>5.48</td><td>17.0</td></tr>
<tr><td rowspan="2">Plasma</td><td>Lotemax 0.5%</td><td>2.08</td><td>0.50</td><td>0.461</td><td>0.910</td></tr>
<tr><td>KPI-121 1%</td><td>1.49</td><td>0.25</td><td>1.52</td><td>2.87</td></tr>
</table>
</td></tr>
</table>

- Using the results from the table above, this reviewer calculated comparative exposure margins. Based on the difference in concentration (0.5% for Lotemax, 1% for KPI-121), a 2-fold exposure margin would be expected.
    - The table below shows that the measured exposure margins were ~ 2x (as expected).

Table 6: Using the comparative tissue concentration results for Lotemax and KPI-121 (report # 2013-068) to calculate tissue-specific exposure margins

Tissue	Exposure margin (KPI-121 divided by Lotemax)	
	C_{max}	$AUC_{0\text{-}6hr}$
Aqueous humor	3.75 x	3.601 x
Cornea	2.737 x	2.604 x
Retina	1.461 x	2.319 x
Plasma	3.297 x	3.153 x

- For completeness-of-record, the results for the other formulations are captured in the table below.

Table 7: Loteprednol etabonate tissue concentrations in rabbits following a single topical ocular dose of Lotemax (0.5%) or a 3 formulations of 1% loteprednol etabonate similar to the clinical drug product (report # 2013-068)

Formulation	Time point	Plasma (ng/ml)	Aqueous humor (ng/ml)	Cornea (ng/ml)	Retina (ng/ml)
Group 1 (Lotemax) 0.5%	5 min	0.242	1.05	632	3.41
	15 min	0.392	4.66	436	3.75
	30 min	0.461	6.88	355	3.15
	1 hr	0.246	4.57	146	2.72
	3 hr	0.0997	0.696	69.9	1.55
	6 hr	0.0452	0.118	22.9	<LLOQ
Group 2 (1.0% LE-MPP, (b) (4)	5 min	1.32	1.39	1730	3.82
	15 min	1.52	11.9	1620	5.19
	30 min	1.14	25.8	706	5.48
	1 hr	0.885	19.9	550	4.85
	3 hr	0.287	1.22	73.8	2.18
	6 hr	0.0897	0.325	81.2	1.23
Group 3 (1.0% LE-MPP (b) (4)	15 min	1.06	12.8	1710	8.90
	30 min	0.906	29.4	840	5.31
	1 hr	1.22	16.4	371	9.91

Reference ID: 4293985

	Group 4 (1.0% LE-MPP, (b) (4)	15 min	1.69	14.0	2030	7.32
		30 min	1.76	26.9	862	6.98
		1 hr	1.42	20.3	640	8.98
Safety endpoints	• Ocular irritation (using the Draize eye irritation scoring system) were recorded pre-dose and prior to each aqueous humor collection. • No treatment-related effects were apparent.					

Title	**Pharmacokinetics of loteprednol etabonate (LE) in aqueous humor following topical dosing with formulations of various concentrations**	
Report #s	• 2012-206 (study laboratory #) • KPI_121-T-001 (Applicant's code #)	
Key findings	• The purpose of this study was to evaluate the PK profile of four different formulations in aqueous humor, following a single topical ocular dose (50 µl/eye) administered to both eyes (OU) • The commercial drug product formulation was not tested • Loteprednol etabonate was detected in the aqueous humor at all time points (up to 12 hours) after a single topical ocular dose. • Elimination from aqueous humor was rapid ($t_{1/2} \leq 1.5$ hours). • No treatment-related ocular irritation was observed	
Report details	Report dates and status	• Study initiated January 7, 2013 • Final report signed March 14, 2013 • Not GLP
	Study laboratory	(b) (4)
	Report location	NDA module 4.2.2.2 Pharmacokinetics: absorption: \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2012-206\2012-206.pdf and \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2012-206\kpi-121-t-001.pdf
Methods	Species	A total of 96 treatment-naïve male New Zealand White rabbits, age range 4.5 to 5.5 months, weight range 2.38 to 3.50 kg
	Dose groups	4 dose groups: 0.4%, 0.5%, 0.6%, 1.0% loteprednol etabonate (24 rabbits/dose)
	Dosing	Single 50 µl topical ocular dose in both eyes
	Sample collection	• Time points: 5, 15, 30 minutes; 1, 3, 6, 9 and 12 hours (3 rabbits/dose/time point)

Reference ID: 4293985

<table>
<tr><td></td><td></td><td>

- Procedure at each time point: anesthetized with isoflurane; 150 µl of aqueous humor collected from each eye

</td></tr>
<tr><td></td><td>Test articles:</td><td>

- Four different formulations were tested. Each had (b) (4)% sodium chloride, (b) (4)% glycerin, (b) (4)% EDTA, and 0.01% BAC.

Table 8: four different formulations of loteprednol etabonate tested in a rabbit topical ocular PK study (report # 2012-206)

<table>
<tr><th>Loteprednol etabonate</th><th>Poloxamer 407</th></tr>
<tr><td>0.4%</td><td rowspan="4">(b) (4)</td></tr>
<tr><td>0.5%</td></tr>
<tr><td>0.6%</td></tr>
<tr><td>1.0%</td></tr>
</table>

- Reviewer notes:
  - None of these are the clinical drug product (described in Table 2 of this review, above). The clinical drug product has (b) (4)% sodium chloride, (b) (4)% glycerin, (b) (4)% EDTA, and 0.01% BAC
  - The clinical drug product also has 1% loteprednol etabonate + (b) (4)% Poloxamer 407

</td></tr>
<tr><td>PK Results:</td><td colspan="2">

Table 9: Aqueous humor PK parameters for the rabbit topical ocular PK study (report # 2012-206)

<table>
<tr><th rowspan="2">Parameter</th><th colspan="4">Loteprednol etabonate concentration</th></tr>
<tr><th>0.4%</th><th>0.5%</th><th>0.6%</th><th>1.0%</th></tr>
<tr><td>Tmax (h)</td><td>0.50</td><td>0.50</td><td>0.50</td><td>0.50</td></tr>
<tr><td>C_{max} (ng/ml)</td><td>28.5 ± 5.7</td><td>36.0 ± 1.2</td><td>59.3 ± 7.1</td><td>60.0 ± 5.7</td></tr>
<tr><td>C_{max} normalized to dose</td><td>71.3</td><td>72.0</td><td>98.8</td><td>60.0</td></tr>
<tr><td>$AUC_{0\text{-last}}$ (ng*h/ml)</td><td>47.8 ± 4.8</td><td>60.4 ± 4.9</td><td>76.5 ± 5.8</td><td>105 ± 10</td></tr>
<tr><td>$AUC_{0\text{-last}}$ normalized to dose</td><td>120</td><td>121</td><td>128</td><td>105</td></tr>
<tr><td>Terminal $t_{1/2}$ (h)</td><td>1.39</td><td>1.50</td><td>1.08</td><td>1.36</td></tr>
</table>

- The authors concluded that the C_{max} showed a plateau between 0.6% and 1.0%, and this reviewer concurs.

</td></tr>
</table>

Reference ID: 4293985

	• The authors noted that AUC was dose proportional from 0.4% to 0.6%
Safety endpoints	• Body weight and ocular irritation (using the Draize eye irritation scoring system) were recorded pre-dose and prior to each aqueous humor collection. • No treatment-related effects were apparent.

Title	**Pharmacokinetics of Loteprednol Etabonate (LE) in Ocular Tissues Following Topical Dosing with Either One of Two LE Test Formulations**	
Report #s	• 2013-030 (study laboratory #) • KPI_121-T-003 (Applicant's code #)	

Key findings	• The purpose of this study was to evaluate the PK profile of two different formulations in aqueous humor, cornea, retina, and plasma following a single topical ocular dose (50 µl/eye) administered to both eyes (OU)
	• The commercial drug product formulation was not tested.
	• Distribution was cornea > aqueous humor > retina > plasma
	  ○ Loteprednol etabonate was detected in retina and plasma after a single topical ocular dose, but cleared rapidly.
	  ○ Loteprednol etabonate was detected in aqueous humor, cornea, and plasma at all time points (up to 12 hours post-dose).
	• No treatment-related ocular irritation was detected.	

Report details	Report dates and status	• Study initiated February 22, 2013 • Final report signed April 30, 2013 • Not GLP
	Study laboratory	(b) (4)
	Report location	NDA module 4.2.2.2 Pharmacokinetics: absorption: \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2013-030\2013-030.pdf and \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2013-030\kpi-121-t-003.pdf
Methods	Species	39 male New Zealand White rabbits. • At time of dosing, they were 6 months old, with a weight range of 2.90 to 4.08 kg. • The rabbits were non-naïve (no reporting on previous exposure).
	Dose groups	0.25 or 1.0% loteprednol etabonate
	Dosing	Single 50 µl topical ocular dose in both eyes

Reference ID: 4293985

<table>
<tr><td></td><td>Sample collection</td><td>

Plasma, aqueous humor, retina and cornea samples were collected from 3 rabbits/time point immediately after euthanasia (i.e. prior to freezing)
A “center punch” retina sample was collected
Samples were collected for both dose levels at 5, 15, 30 minutes, 1, 3, 6, 12 hours
Additionally, samples were collected for the 1% dose at 12 hours (time point omitted for the 0.25% group)

</td></tr>
<tr><td></td><td>Test articles:</td><td>

Two different formulations were tested (different from the formulations tested in report # 2012-206, reviewed above). Both had (b) (4)% sodium chloride, and (b) (4)% EDTA. (b) (4) glycerin.

Table 10: two different formulations of loteprednol etabonate tested in a rabbit topical ocular PK study (report # 2013-030)
<table>
<tr><th>Loteprednol etabonate</th><th>Poloxamer 407</th><th>BAC</th></tr>
<tr><td>1.0%</td><td rowspan="2">(b) (4)</td><td>0.01%</td></tr>
<tr><td>0.25%</td><td>(b) (4)%</td></tr>
</table>

Reviewer notes:

None of these are the clinical drug product (described in Table 2 of this review, above). The clinical drug product has (b) (4)% sodium chloride, (b) (4)% glycerin, (b) (4)% EDTA, and 0.01% BAC
The clinical drug product also has 1% loteprednol etabonate + (b) (4)% Poloxamer 407

</td></tr>
<tr><td>PK Results:</td><td colspan="2">

Following topical ocular dosing, loteprednol rapidly distributed into the eye, and was detectable in all tissues at 5 minutes post-dose.
For the retina, the elimination half-life could not be calculated:

For 1%, loteprednol etabonate was detected in 5/6 retinas at 5 minutes, in all retinas from 15 minutes to 3 hours. It was detected in 5/6 retinas at 6 hours, and 1/6 at 12 hours.
For 0.25%, loteprednol was detected in in 5/6 retinas at 5 minutes, and in most retinas from 15 minutes to 1 hour. It was not detected in any retinas at 3 or 6 hours.

<table>
<tr><th rowspan="2">Sample</th><th rowspan="2">Parameter</th><th colspan="2">Loteprednol etabonate concentration</th></tr>
<tr><th>1.0%</th><th>0.25%</th></tr>
<tr><td rowspan="3">Aqueous humor</td><td>C_{max} (ng/ml)</td><td>25.20</td><td>13.40</td></tr>
<tr><td>$AUC_{0\text{-}last}$ (ng*hr/ml)</td><td>38.40</td><td>22.20</td></tr>
<tr><td>T_{max} (h)</td><td>0.5</td><td>0.5</td></tr>
</table>
</td></tr>
</table>

		$t_{1/2}$ (h)	2.66	0.76
	Cornea	C_{max} (ng/g)	2190	1480
		$AUC_{0\text{-last}}$ (ng*h/g)	3260	1070
		T_{max} (h)	0.083	0.083
		$t_{1/2}$ (h)	2.35	2.66
	Plasma	C_{max} (ng/ml)	1.73	1.70
		$AUC_{0\text{-last}}$ (ng*hr/ml)	5.03	3.24
		T_{max} (h)	0.5	0.25
		$t_{1/2}$ (h)	2.47	1.30
	Retina	C_{max} (ng/g)	7.85	5.93
		$AUC_{0\text{-last}}$ (ng*h/g)	22.5	3.0
		T_{max} (h)	0.25	0.083
		$t_{1/2}$ (h)	3.15	Not calculable
Safety endpoints	• Ocular irritation was scored, using a Draize Eye Irritation Scoring scale, prior to dosing and prior to each aqueous humor sampling. ○ *Reviewer note*: presumably, eyes were evaluated immediately prior to euthanasia. However, this is not stated explicitly in the study report. • No ocular irritation was detected for any eye, at any time point.			

Reference ID: 4293985

Title	**Pharmacokinetics of Loteprednol (1%) of Various Particle Size Administered Topically in a MPP Formulation**	
Report #s	• 2013-150 (study laboratory #) • KPI_121-T-022 (Applicant's code #)	
Key findings	• This study tested a formulation close to (but not exactly) the clinical drug product formulation. • The purpose of the study was to compare 5 different particle sizes of loteprednol etabonate (b) (4) mean diameter) at 1% loteprednol etabonate. • Rabbit received a single topical ocular dose (50 µl/eye) administered to both eyes (OU). Drug substance concentrations in the cornea, aqueous humor, palpebral conjunctiva, retina, and plasma were measured. • Distribution was: cornea > palpebral conjunctiva > aqueous humor > retina > plasma • Smaller particle size correlated with higher C_{max} values for the cornea, aqueous humor, conjunctiva, and retina. • No treatment-related ocular irritation was detected.	
Report details	Report dates and status	• Study initiated September 9, 2013 • Final report signed October 23, 2013 • Not GLP
	Study laboratory	(b) (4)
	Report location	NDA module 4.2.2.2 Pharmacokinetics: absorption: \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2013-150\2013-150.pdf and \\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\422-pk\4222-absorp\2013-150\kpi-121-t-022.pdf
Methods	Species	60 male New Zealand White rabbits. • At time of dosing, they were 6 to 7 months, with a weight range 2.61 to 3.46 kg • The rabbits were treatment-naive
	Dose groups	1.0% loteprednol etabonate
	Dosing	Single 50 µl topical ocular dose in both eyes
	Sample collection	Plasma, aqueous humor, cornea, retina (center punch), and palpebral conjunctiva were collected from 3 rabbits/time point immediately after euthanasia (i.e. prior to freezing) at 0.5, 1, 2 and 4 hours post-dose
	Test articles:	• One formulation was tested: (b) (4)% sodium chloride, (b) (4)% glycerin, (b) (4)% sodium citrate dihydrate, (b) (4)% poloxamer 407, (b) (4)% citric acid, (b) (4)% edetate disodium. • The clinical drug product has (b) (4)% EDTA, and 0.01% benzalkonium chloride. The formulations are otherwise the same.

- Five different particle sizes of loteprednol etabonate were tested, reported as the D50 (d50; mass median diameter):

Table 11: five different particle sizes of 1% loteprednol etabonate tested in a rabbit topical ocular PK study (report # 2013-150)

Formulation	Particle size (D50) (nm) (b) (4)
#1	
#2	
#3	
#4	
#5	

PK Results:

- Following topical ocular dosing, loteprednol was detected in all samples, up to 4 hours. Distribution was cornea > palpebral conjunctiva > aqueous humor > retina > plasma.
- The authors calculated C_{max} and $AUC_{0\text{-}4hours}$. This reviewer identified the Tmax values from the individual sample data.
- For the cornea, the authors note that the smaller particle sizes (formulations #1 and 2) resulted in higher C_{max} than the larger particle sizes.
- The Applicant noted (NDA module 2.6.4 Pharmacokinetic Summary) that the same trend is apparent for slightly increased concentrations with decreasing particle size for the aqueous humor, palpebral conjunctiva, and retina.

Table 12: Rabbit Tissue and plasma C_{max} values for topical ocular dosing with 5 different particle sizes of 1% loteprednol etabonate (report # 2013-150)

Maximum Concentration (Cmax) in ng/mL or ng/g	Plasma	Palpebral Conjunctiva	Cornea	Aqueous Humor	Center-Punch Retina
Formulation #1	1.75	868	1660	29.7	8.74
Formulation #2	1.20	670	1230	21.9	6.34
Formulation #3	1.34	305	672	15.5	5.37
Formulation #4	1.29	446	713	14.3	4.44
Formulation #5	1.58	324	577	11.3	4.77

Table 13: Rabbit Tissue and plasma $AUC_{0\text{-}4}$ values for topical ocular dosing with 5 different particle sizes of 1% loteprednol etabonate (report # 2013-150)

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	Area Under the Curve ($AUC_{0\text{-}4\ h}$) in ng*h/mL or ng*h/g / **Plasma** / **Palpebral Conjunctiva** / **Cornea** / **Aqueous Humor** / **Center-Punch Retina** Formulation #1 / 3.15 / 1610 / 2080 / 35.8 / 17.8 Formulation #2 / 3.05 / 1470 / 2180 / 28.6 / 14.2 Formulation #3 / 2.81 / 411 / 881 / 21.1 / 10.9 Formulation #4 / 2.70 / 1130 / 1300 / 18.5 / 10.7 Formulation #5 / 2.77 / 507 / 695 / 14.8 / 8.94
Clinical drug product particle size	• The NDA (module 2.3.P.5 Control of Drug Product[18]) reports that particle size of the clinical drug product is measured by dynamic light scattering. The means of the d10, d50, and d90 are reported. • The NDA (module 3.2.P.5 Control of Drug Product: Specifications[19]) reports that the acceptance criteria include: ○ d10: (b) (4) ○ d50: ○ d90: • Therefore, t ormulations 1 and 2.
Safety endpoints	• Ocular irritation was scored, using a Draize Eye Irritation Scoring scale, prior to dosing and prior to each aqueous humor sampling. ○ *Reviewer note*: presumably, eyes were evaluated immediately prior to euthanasia. However, this is not stated explicitly in the study report. • No ocular irritation was detected for any eye, at any time point.

Schopf et al. 2014[20]	• LE-MPP 0.4% (a code name for KPI-121) was compared against commercial Lotemax (loteprednol etabonate ophthalmic suspension 0.5%). • Note: the formulation contained 0.01% BAC, but was not otherwise described. This is a serious study limitation. Since the other rabbit studies did not test the final clinical drug product for KPI-121, this reviewer presumes that this experiment also failed to test the exact clinical drug product. • Design corresponds to the reports reviewed above:

[18] NDA module 2.3.P.5 accessed via: \\cdsesub1\evsprod\nda210565\0001\m2\23-qos\23p-drug-prod\drug-product-contr.pdf
[19] NDA module 3.2.P.5.1 accessed via: \\cdsesub1\evsprod\nda210565\0001\m3\32-body-data\32p-drug-prod\kpi-121\32p5-contr-drug-prod\32p51-spec\specifications.pdf
[20] Schopf L, Enlow E, Popov A, Bourassa J, Chen H. 2014. Ocular pharmacokinetics of a novel loteprednol etabonate 0.4% ophthalmic formulation. Ophthalmol Ther. 3:63-72. The paper was submitted to the NDA, and is also available via: https://www.ncbi.nlm.nih.gov/pubmed/25134493

- A total of 48 male New Zealand White rabbits were used (age 4-5 months, weight range 2.41 to 3.33 kg).
- Rabbits received a single 50 µl drop OU.
- Groups of 3 rabbits/dose/ time point were sacrificed at 5, 15, 3 minutes, 1, 3, 6 and 12 hours.
- PK for aqueous humor, conjunctiva, cornea, iris/ciliary body, and central retina.
- Ocular irritation was assessed pre-dose and prior to each necropsy.

- Loteprednol etabonate concentrations were higher for LE-MPP 4% than for Lotemax 0.5% for all tissues analyzed.

Table 14: Ocular PK comparison for Lotemax (loteprednol etabonate ophthalmic suspension 0.5%) versus LE-MPP 0.4% (reported in Schopf et al. 2014)

Table 1 Pharmacokinetic parameters (mean ± SEM) for loteprednol etabonate following a s 0.5% or LE-MPP 0.4% in New Zealand White rabbits

Sample	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL or ng/g)	AUC_{0-last} (ng h/mL or ng h/g)
Aqueous humor				
Lotemax 0.5%	2.31	0.50	6 ± 1	14 ± 2
LE-MPP 0.4%	1.57	0.50	20 ± 3	31 ± 1
Cornea				
Lotemax 0.5%	3.75	0.083	621 ± 56	1130 ± 173
LE-MPP 0.4%	1.89	0.083	2260 ± 470	1670 ± 130
Conjunctiva				
Lotemax 0.5%	4.26	0.083	1130 ± 177	1610 ± 238
LE-MPP 0.4%	1.92	0.083	2930 ± 250	1610 ± 140
Iris/Ciliary body				
Lotemax 0.5%	3.04	0.50	49 ± 6	91 ± 5
LE-MPP 0.4%	1.49	0.25	137 ± 14	206 ± 10
Retina (center punch)				
Lotemax 0.5%	9.18	0.50	2.1 ± 0.2	6.9 ± 1.3
LE-MPP 0.4%	1.55	0.50	6.8 ± 1.2	14.7 ± 1.8
Plasma				
Lotemax 0.5%	1.88	0.25	0.33 ± 0.06	0.76 ± 0.06
LE-MPP 0.4%	1.71	0.25	1.19 ± 0.26	2.12 ± 0.27

- No treatment-related ocular irritation was reported.

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	• The NDA's Pharmacokinetic Written Summary (module 2.6.4) mentions this paper, stating that the experiments were "conducted by Kala". • It is not clear why the results were not submitted to the NDA as a study report. Based on the other data available, this paper is not needed to support the safety of Inveltys; no Information Request was sent. The results do provide additional context.

6 General Toxicology

The Applicant submitted one toxicology study for KPI-121: report # 8286658. The Applicant also provided a separate report (report # KPI-121-T-005 Technical Report) describing the test article characterization.

6.2 Repeat-Dose Toxicity

Study title: 28-Day ocular instillation toxicity and toxicokinetic study with KPI-121 in rabbits	
Study numbers:	• 85886658 (study laboratory code) • KPI-121-N-001-P (Applicant's code)
Study report location:	NDA module 4.2.3.2 Toxicology: repeat-dose toxicity: rabbit (\\cdsesub1\evsprod\nda210565\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8286658\kpi-121-t-005-body.pdf)
Conducting laboratory and location:	(b) (4)
Test site for histopathology:	
Report date and status	December 23, 2013. Final report.
Date of study initiation:	July 9, 2013
GLP compliance:	Yes, signed
QA statement:	Yes, signed
Drug, lot #, and % purity:	KPI-121 1.0%, lot # JB2_31, purity 99.1%

Key Study Findings

- Groups of 3/sex New Zealand White (NZW) rabbits were dosed with 0 or 1% KPI-121 four times daily (QID) in both eyes for 28 days. The test article was well-tolerated, and no dose-limiting toxicities were observed.
- Endpoints were clinical observations, body weight, ocular irritation, ophthalmology (pre-dose, D2 and D28), clinical pathology (at necropsy on D29),

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standard gross pathology, selected organ weights, limited histopathology (eye and adnexa), and plasma toxicokinetics (TK).

- Treatment-related pharmacological activity was observed at the single test dose:
  - decreased body weight (-7% by D29) for males and females
  - Higher mean corpuscular volume and mean corpuscular hemoglobin (males)
  - Decreased absolute lymphocyte counts (both sexes)
  - Higher glucose (males)
  - Higher triglycerides (both sexes)
  - Higher aspartate aminotransferase and alanine aminotransferase (females)
  - Organ weight changes: adrenal, spleen, and thymus (both sexes); prostate/seminal vesicle gland
  - Histology (both sexes): adrenal cortex atrophy; eyelid decreased anagen hair follicles
- The authors considered the effects on spleen and thymus correlated with decreased lymphocyte counts, and to be potentially adverse. The authors also considered the adrenal cortical atrophy to be potentially adverse, since reversibility was not assessed. This reviewer concurs; therefore, a no observed adverse effect level (NOAEL) was not identified.

Methods	
Doses:	• 0 (vehicle) or 1% KPI-121 • The dose is the equivalent of: ○ (b) (4) mg/eye/dose ○ (b) (4) mg/eye/day ○ (b) (4) mg/rabbit/day
Frequency of dosing:	Four times daily (QID), spaced 3 hours ± 15 minutes apart, in both eyes (OU) for 28 days
Route of administration:	• Topical ocular instillation • "placing a drop of formulation in the sac formed by extending the lower eyelid. After administration, the eye was gently held closed for approximately 3 seconds to distribute the dose" • A fresh bottle was opened for each dose, and was shaken "thoroughly (for at least 5 seconds) by hand" prior to dosing interval.
Dose volume:	One (b) (4) µl per dose ((b) (4) µl/eye/day)
Formulation/Vehicle:	Drug product vehicle: (b) (4) % glycerin, (b) (4) % Poloxamer 407, (b) (4) % sodium citrate dehydrate, (b) (4) % sodium edetate dehydrate, (b) (4) % anhydrous citric acid, 0.01% benzalkonium chloride
Species/Strain:	Rabbit / New Zealand White

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Number/Sex/Group:	3/sex/dose (necropsied on D29)
Age at start of dosing:	14 weeks
Weight at start of dosing:	Males 2695 to 2830 g Females 2563 to 2850 g
Satellite groups:	None
Deviation from study protocol:	None that this reviewer considers important to the interpretation of the study [protocol deviations are documented on report page 36]

Observations and Results

Mortality

- No premature mortality. All animals survived to the scheduled necropsy on D29.
- Checks for morbidity and mortality were done twice daily.

Clinical Signs

- No treatment-related effects apparent.
- Clinical observations were checked once daily
- Detailed observations were done weekly
- After the first and last dose, animals were observed for at least 1 minute post-dose for signs of ocular discomfort

Body Weights

- Treatment-related decreased weight gain was apparent throughout dosing for both sexes (statistically significant for males from D11 onward). The authors considered this effect treatment-related and consistent with expected pharmacology. From D1 to D29:
  - Control males gained 8.5% body weight. Treated males gained 1.8% body weight.
  - Control females gained 11.0% body weight. Treated females gained 2.8% body weight.
- Body weight was measured pre-dose and prior to dosing on D1, 5, 8, 11, 15, 22, 25 and 29.

Table 15: Body weight means for the 28-day rabbit ocular toxicology study (report # 8286658)

Day	Males		Females	
	0	1% KPI-121 QID	0	1% KPI-121 QID
1	2774 ± 28	2743 ± 76	2686 ± 46	2705 ± 144
5	2765 ± 40	2729 ± 53	2699 ± 62	2690 ± 134
8	2777 ± 33	2721 ± 65	2717 ± 79	2656 ± 152
11	2845 ± 21	2737 ± 28 *	2750 ± 73	2694 ± 124
15	2894 ± 18	2760 ± 30 *	2839 ± 90	2740 ± 110
18	2927 ± 20	2776 ± 18 *	2874 ± 81	2752 ± 137
22	3005 ± 81	2808 ± 29 *	2938 ± 72	2805 ± 112

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25	2979 ± 97	2835 ± 6 *	2950 ± 84	2795 ± 135
29	3009 ± 67	2792 ± 24 *	2982 ± 130	2780 ± 128

Data presented as mean ± standard deviation.
* : P ≤ 0.05, statistically significant using the two-sample t-test.

Feed Consumption

- No treatment-related effects apparent
- Pre-dose, rabbits were presented with increasing amounts of food once daily, until they acclimated to 150 g/day. Animals were then maintained on 150 g/day
- Food consumption was assessed qualitatively once daily, and presented as part of clinical signs.

Ophthalmoscopy

- No treatment-related effects apparent
- Ocular irritation was scored using a modified Draize scale for scoring ocular lesions. Scoring was done pre-dose and during the dosing phase (D1, 5, 8, 11, 15, 18, 22, 25, 28) prior to the first daily dose, ~ 30 minutes prior to the last daily dose, and 30 minutes to 1 hour after the last daily dose
- Slit lamp biomicroscopy with corneal fluorescein staining was conducted pre-dose, and during the dosing phase on D2 and D28 (2 hours ± 30 minutes after the first daily dose): to evaluate the cornea, adnexa and anterior portions
- Indirect ophthalmology was evaluated at pre-dose and D28 only (i.e. not D2) with dilation to evaluate the ocular fundus
- *Reviewer note*: neither intraocular pressure (IOP) nor electroretinography (ERG) were measured.

Hematology and Clinical Chemistry

- Blood collected pre-dose and D29, without fasting, for hematology, coagulation, and clinical chemistry
- No urine was collected for urinalysis

- Treatment decreased absolute lymphocyte counts. Comparing treated to controls for D29:
  - -18.0% for males (statistically significant)
  - -24.1% for females (statistically significant)
  - [*Reviewer note*: % lymphocyte counts not reported]

- Treatment increased triglyceride levels. Comparing treated to controls for D29:
  - 2.2-fold increase for males (statistically significant)
  - 3.5-fold increase for females (statistically significant)

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- The authors identified slightly increased glucose (+14.0% in treated males compared to control males on D29) as treatment related based on expected pharmacology for loteprednol etabonate.

Table 16: Selected hematology and clinical chemistry results for the 28-day rabbit ocular toxicology study (report # 8286658)

Parameter	Day	Male		Female	
		0	1% KPI-121 QID	0	1% KPI-121 QID
Absolute lymphocyte count (E^3/µl)	D-10	7.65 ± 0.697	7.72 ± 1.553	5.43 ± 0.962	7.36 ± 0.694
	D29	6.62 ± 0.778	5.43 ± 0.381 *	4.97 ± 0.825	3.77 ± 0.771 *
Triglyceride (mg/dl)	D-10	60 ± 19.7	46 ± 1.5	46 ± 14.0	53 ± 13.6
	D29	64 ± 20.3	142 ± 83.9 *	40 ± 9.6	182 ± 72.9 *
Glucose (mg/dl)	D-10	120 ± 8.0	118 ± 4.6	133 ± 6.8	130 ± 14.4
	D29	121 ± 3.8	138 ± 2.6	122 ± 6.8	129 ± 7.8

D-10 = pre-dose
Data presented as means ± standard deviation
* Statistically significant by two-sample t-test

Gross Pathology

- No treatment-related effects apparent
- On D29, full gross pathology was performed: “external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues”

Organ Weights

- A limited panel of organs were weighed: adrenal, brain, epididymis, drained gall bladder, heart, kidneys, liver, lungs with large bronchi, ovaries, pituitary gland, prostate, mandibular salivary glands, seminal vesicle, spleen, testes, thymus, thyroids with parathyroids, and uterus.

- Treatment decreased the adrenal, spleen, thymus and prostate/seminal vesicle gland weight. The authors considered these effects consistent with systemic corticosteroid exposure.
  - Spleen and thymus effects correlated with hematology (decreased absolute lymphocyte counts)
  - Adrenal histology (atrophy) correlated with decreased organ weight
  - No histology for the spleen, thymus, or prostate/seminal vesicle
- From page 25 of the study report:

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Table 17: 1% KPI-121 decreased adrenal, spleen, thymus and prostate/seminal vesicle weight in the 28-day rabbit topical ocular toxicology study (report # 8286658)

Organ	Parameter	Male		Female	
		0	1% KPI QID	0	1% KPI QID
Adrenal	Absolute Weight (g)	0.322	65*	0.314	71
	Body Weight Ratio (%)	0.0110	69	0.0109	74
	Brain Weight Ratio (%)	3.4337	67*	3.2942	75
Spleen	Absolute Weight (g)	1.445	57*	1.298	69
	Body Weight Ratio (%)	0.0494	62*	0.0445	74
	Brain Weight Ratio (%)	15.4690	60*	13.4630	75
Thymus	Absolute Weight (g)	3.530	76	3.928	42*
	Body Weight Ratio (%)	0.1206	82	0.1370	44*
	Brain Weight Ratio (%)	37.8389	80	40.5170	46*
Prostate + seminal vesicle	Absolute Weight (g)	3.932	73*	[not applicable for females]	
	Body Weight Ratio (%)	0.1345	78*		
	Brain Weight Ratio (%)	41.9550	76*		

Note: Statistical analysis was ANOVA and Leven's test, $p \leq 0.05$

Histopathology

Based on Battery limited to: adrenals, eye with bulbar conjunctivae, upper and lower eyelids with palpebral conjunctivae, gross lesions, Harderian gland, lacrimal gland, nictitating membrane.

The Applicant listed NDA 20583 (Lotemax®), and is relying on FDA's previous finding of safety and efficacy for loteprednol etabonate. Based on the previously available safety information for loteprednol, and corticosteroids as a class, P/T concurs that this study's focus on select target tissues is adequate to support safety.

Peer Review: No. The study pathologist was (b) (4)

Histological Findings:

- The authors noted treatment-related changes: adrenal cortex atrophy, and anagen hair follicles of the eyelids.

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- Note: Anagen is the active growth phase of hair follicles. Catagen is a short phase after anagen, followed by telogen (the resting/dead phase of the hair follicle)
- Note: Anagen was scored as present/absent (i.e. no severity rating). The pathologist did not explicitly mention catagen or telogen (i.e. not clear whether less anagen means more telogen, or more fewer total hairs)
- Note: adrenal atrophy was more severe in males (moderate for 3/3) versus females (slight for 3/3)
- Reviewer note: the spleen and thymus were not examined microscopically. Based on the observed changes in hematology (decreased lymphocyte count) and organ weights, as well as general scientific knowledge for corticosteroid activity, this reviewer presumes that 1% KPI-121 caused atrophy and lymphoid depletion in both the spleen and thymus.

Table 18: Treatment-related adrenal cortex atrophy and decreased eyelid anagen hair follicles detected at histology in the 28-day rabbit toxicity study (report # 8286658)

Lesion	Severity	Male		Female	
		0	1% KPI-121	0	1% KPI-121
# of rabbits examined		3	3	3	3
Adrenal cortex atrophy	Slight	0	0	0	3
	moderate	0	3	0	0
Eyelid, upper left Anagen hair follicles, decreased	Present	0	3	0	3
Eyelid, lower left Anagen hair follicles, decreased	Present	0	3	0	2
Eyelid, upper right Anagen hair follicles, decreased	Present	0	3	0	3
Eyelid, lower right Anagen hair follicles, decreased	Present	1	3	0	3

Toxicokinetics

- Blood was collected pre-dose, on D1 (approximately 5 15 30 minutes, 1, 2 and 3 hours after the first daily dose), on D28 pre-dose (prior to the last daily dose) and then after the last daily dose at 15, 30 minutes, 1, 3,6 and 12 hours
- From page 22 of the study report:

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Table 19: Plasma TK results for the 28-day topical ocular rabbit toxicology study (report # 8286658):

Day	Sex	C_{max} (ng/ml)	T_{max} (hr)	$AUC_{0\text{-}3hours}$ (ng*hr/ml)	$AUC_{0\text{-}t}$ (ng*hr/ml)
1	M	4.69 ± 0.802	0.250 ± 0	3.89 ± 0.996	3.89 ± 0.996
	F	4.09 ± 0.794	0.500 ± 0	3.45 ± 0.596	3.45 ± 0.596
28	M	7.97 ± 0.701	0.357 ± 0.129	6.14 ± 0.250	8.78 ± 1.72
	F	3.11 ± 0.483	0.350 ± 0.132	3.22 ± 0.339	4.44 ± 0.657

Data presented as means ± standard deviation
The dose was 1% KPI-121 QID (b) (4) OU

- Authors concluded that KPI-121 was rapidly absorbed (based on the quick T_{max}) and concluded that no accumulation was apparent.
- This reviewer notes that males had a higher C_{max} and AUC at D28, consistent with the treated males exhibiting slightly greater treatment-related effects compared to females (decreased body weight; adrenal and spleen weights).

Dosing Formulation Analysis

- The (b) (4) study report (report # 8286658) included certificates of analysis for the drug product (report pages 526-530), and included analysis of the vehicle for benzalkonium chloride (b) (4)% of nominal).
- Additionally, Kala provided a report titled "KPI 121-Toxicology Formulations" (report # KPI-121-T-005) that described the vehicle, and purification process. The test article was (b) (4) toward ensuring that the toxicology test article fully qualified the drug product for the intended shelf-life. The 1% loteprednol etabonate final test article had:
  - Loteprednol etabonate, (b) (4)% of nominal
    (b) (4)

7 Genetic Toxicology

The Applicant did not conduct genetic toxicology studies. The Applicant is relying on the Agency's finding of safety and effectiveness for Lotemax® (NDA 20583), as described in published labeling. The labeling for Lotemax® (NDA 20583) reports that loteprednol etabonate was not genotoxic in the Ames assay, the mouse lymphoma tk assay, a chromosomal aberration assay in human lymphocytes, or in the *in vivo* mouse micronucleus assay.

8 Carcinogenicity

The Applicant did not conduct carcinogenicity studies for KPI-121. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. P/T concurs that carcinogenicity studies are not warranted to support the indicated duration of use (i.e. 2 weeks).

9 Reproductive and Developmental Toxicology

The Applicant did not conduct reproductive toxicology, developmental toxicology, or fertility studies. The Applicant is relying on the Agency's finding of safety and effectiveness for Lotemax® (NDA 20583), as described in published labeling. The labeling for Lotemax® (NDA 20583) is not yet PLLR-compliant.

This reviewer's recommended labeling for Inveltys (above in this review) is PLLR-compliant, based on the studies submitted to NDA 20583 (the same studies were also submitted to NDA 202872).

Regulatory notes: DTOP anticipates that the PLLR labeling for NDA 202872 (Lotemax) will be approved prior to labeling negotiations with Kala.

- The rat peri- postnatal study was not previously mentioned in approved labeling: i.e. the PLLR conversion for NDA 202872 (Lotemax) will be the first label summarizing the study.
- For previous loteprednol etabonate labeling, the fertility section misstated the dose which affected female fertility (i.e. previously reported 50 mg/kg, should be 25 mg/kg).

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11 Integrated Summary and Safety Evaluation

- In consultation with FDA's Division of Transplant and Ophthalmology (DTOP), the Applicant designed nonclinical studies to demonstrate safety for Inveltys, directly and by bridging to Lotemax.
- The rabbit studies submitted by the Applicant show that topical ocular dosing of Inveltys:
    - Results in rapid distribution of loteprednol etabonate: cornea > conjunctiva > aqueous humor > retina > plasma. Clearance is rapid (consistent with the need to dose at least BID for clinical efficacy)
    - Is well tolerated, causing systemic effects (weight loss, lymphocyte depletion, adrenal cortex atrophy) but not detectable ocular irritation.
    - *Reviewer note*: the lack of ocular irritation is consistent with intended pharmacology.
- The NDA for Inveltys is submitted under the 505(b)(2) pathway, listing NDA 20583 for Lotemax (Loteprednol etabonate 0.5%) ophthalmic suspension/drops. Drugs@FDA has the original 1998 labeling[21]. Additionally, the Applicant submitted 2016 labeling[22], which is published at Accessdata.fda.gov[23] but which was not reviewed by DTOP.
- For both approved Lotemax, and for Inveltys, the clinical indication is "treatment of postoperative inflammation and pain following ocular surgery".
    - The Clinical review discipline has explained (Boyd/McDougal, personal communication) that loteprednol would generally only be prescribed for one eye. If the patient needed surgery on both eyes at the same time, loteprednol would generally not be prescribed.
    - Therefore, the calculations below assume treatment of only one eye.

11.1 Ocular safety margin for Inveltys

- The 28-day rabbit topical ocular study (report # 8286658) compared vehicle to one dose level of the test article, 1% loteprednol etabonate QID OU, which was well-tolerated.
    - Treatment-related systemic effects (body weight, hematology, adrenal, spleen, prostate) were detected at the tested dose.
    - No NOAEL was established.

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[21] NDA 20583. Labeling dated 3/09/1998, accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20583lbl.pdf

[22] NDA module 1.14.3 Listed drug labeling, \\cdsesub1\evsprod\nda210565\0001\m1\us\114-label\1143-list-drug-label\lotemax-pi-2016.pdf

[23] Labeling for "LOTEMAX- loteprednol etabonate suspension/ drops Bausch & Lomb Incorporated" revised 9/2016, accessed via: https://www.accessdata.fda.gov/spl/data/ae27f407-c1da-4141-8281-2c89ef9ec1fa/ae27f407-c1da-4141-8281-2c89ef9ec1fa.xml

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- This study is the same concentration (1%) and drug formulation as the marketed product, Inveltys. Therefore, the safety margin is 1x (by concentration) or 2x (by daily dose). The calculated exposure margins are overly-protective, because rabbits were dosed QID for 28 days while patients will use the product BID for 14 days.

Table 20: Safety margins for ocular toxicity of Inveltys

Dose level tested in the rabbit topical ocular toxicity study (report # 8286658): 1% KPI OU QID	Safety margin for Inveltys (loteprednol etabonate) 1% based on strength	Safety margin for Inveltys (loteprednol etabonate) 1% based on daily dose
1% loteprednol etabonate = (b) (4) mg/eye/dose = (b) (4) mg/eye/day = (b) (4) mg/rabbit/day	1x	2 x

11.1 Systemic dose margin for Inveltys based on the Applicant's data

- As noted above, the 28-day topical ocular rabbit toxicity study (report # 8286658) observed treatment-related effects at the dose level tested, 1% KPI-121 (equivalent to (b) (4) mg/rabbit/day of loteprednol etabonate). This dose level caused treatment-related systemic toxicity consistent with the corticosteroid class: weight loss, adrenal cortical atrophy, lymphocyte depletion, spleen and thymus weight loss.
- The Applicant reports that the dropper bottle tip delivers a volume of (b) (4) µl per drop (NDA module 3.2.P.1 Description and Composition of the Drug Product).
- The labeling dosage is twice daily (BID), one or two drops per dose. Assuming 2 drops/dose, the clinical daily dose of Inveltys is (b) (4) mg/person/day.
- Based on the 2005 Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers[24] and assuming 100% absorption of the administered topical ocular dose:
  - Using the rabbit reference body weight of 1.8 kg, and the rabbit conversion factor of 12, the rabbit dose of (b) (4) mg/rabbit/day = (b) (4) mg/kg/day = (b) (4) $mg/m^2/day$.
  - Using the human reference body weight of 60 kg, and the human conversion factor of 37, the clinical dose of (b) (4) mg/person/day = (b) (4) mg/kg/day = (b) (4) $mg/m^2/day$.
  - The dose margin from the rabbit LOAEL to the clinical dose is 21.6 x.

[24] Accessed via: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078932.pdf

Table 21: Systemic dose margin from the LOAEL of the rabbit 28-day topical ocular toxicity study (report # 8286658)

Units	Rabbit LOAEL	Clinical dose
Strength of KPI-121	1%	1%
Frequency of dosing	QID both eyes	BID single eye
Daily dose	(b) (4) mg/rabbit/day	(b) (4) mg/person/day
	(b) (4) mg/kg/day	(b) (4) mg/kg/day
	(b) (4) mg/m^2/day	(b) (4) mg/m^2/day
Dose margin (mg/m^2 basis)		21.62 x

11.1 Systemic dose margin for Inveltys based on the listed drug (NDA 20583 Lotemax)

- For Lotemax (NDA 20583),:
  - The strength is 0.5% loteprednol etabonate;
  - The approved dosage and administration is "Apply one to two drops of LOTEMAX into the conjunctival sac of the (b) (4) eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period."
  - Labeling summaries clinical pharmacology: "Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with LOTEMAX."
- For KPI-121 (Inveltys),
  - The strength is 1% (10 mg/ml) loteprednol etabonate
  - The proposed dosage and administration is "Instill one to two drops of INVELTYS™ into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period."
  - The proposed clinical PK language for labeling includes: "Following twice-daily unilateral topical ocular dosing of INVELTYS™ for 14 days in (b) (4), the plasma concentrations of loteprednol etabonate and its metabolites (PJ-91 and PJ-90) were below the limit of quantitation (b) (4) at all test points."
- The daily doses are equivalent: (b) (4)
  - Therefore, the dose margin from Lotemax to Inveltys is 1x (on a dose basis).

- From a P/T perspective, this approach is adequate to establish 505(b)(2) reliance on the listed drug.

- Because clinical PK did not detect loteprednol etabonate of its metabolites in blood for either Lotemax or Inveltys, the finding of systemic safety for Lotemax is adequate to establish the systemic safety for Inveltys.
  - From a P/T perspective, this approach would also be adequate *per se* to establish 505(b)(2) reliance on the listed drug.

11.3 Dose margins for labeling

- The NDA for Inveltys is submitted under the 505(b)(2) pathway, listing NDA 20583 for Lotemax (Loteprednol etabonate 0.5%) ophthalmic suspension/drops.
- For NDA 20583, the application included study reports for rabbit embryofetal developmental toxicity, rat embryofetal developmental toxicity, rat fertility and general reproductive performance, rat peri/post-natal development, and genotoxicity. These same study reports were submitted to each of the Lotemax NDAs.
- The PLLR review of these studies was conducted recently for NDA 202872 (Lotemax).
  - For each loteprednol etabonate NDA, PLLR review should consider the drop size, whether dosing is indicated for one or both eyes, and the number of drops per day.
  - Adjustment is warranted based on clinical drop volume (i.e. clinical dose).
  - For NDA 202872, the reported clinical drop size was (b) (4) µl. For Inveltys, the clinical drop size is (b) (4) µl.
  - Adequate TK data are not available for these study reports, and therefore dose margins are calculated based on body surface area.

Table 22: Dose margins for Inveltys™ labeling


(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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07/19/2018

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07/19/2018