Summary Report

Prednisolone Acetate

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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REVIEW OF NOMINATION

Prednisolone acetate (UNII code: 8B2807733D) was nominated for inclusion on the 503B Bulks List by Fagron as an 1 % ophthalmic suspension to manage symptoms associated with acute anterior uveitis.

Reasons provided for nomination to the 503B Bulks List include prednisolone acetate being a more effective option than other steroid products to treat acute anterior uveitis and the need to avoid potential allergens in ophthalmic solutions. Additionally, benzalkonium chloride, the preservative in all FDA-approved ophthalmic solutions, and sulfite are both potential allergens that patients may need to avoid.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of prednisolone acetate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for prednisolone acetate; name variations of prednisolone acetate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing prednisolone acetate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Prednisolone acetate is a component of an FDA-approved product. The desired compounded products identified in the submitted nomination do not substantially differ from the commercially available product; therefore, a systematic literature review was not conducted.

Outreach to medical specialists and specialty organizations

Using the indication from the nomination, one (1) medical specialty that would potentially use prednisolone acetate was identified: ophthalmology. Semi-structured interviews were conducted with subject matter experts within this specialty. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. One (1) expert was contacted for an interview, of which one (1) accepted and zero (0) declined. The interview was recorded and transcribed via ©Rev.com. QSR International's NVivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for ophthalmology, identified from the nomination and interview, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to five (5) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Ophthalmology	American Academy of Ophthalmology (AAO)
	American Society of Cataract and Refractive Surgery (ASCRS)
	American Society of Retina Specialist (ASRS)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Prednisolone acetate is available as an FDA-approved product.
- Prednisolone acetate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for prednisolone acetate.
- Prednisolone acetate is available in Abu Dhabi, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date
Prednisolone acetate	0.12%, 1%	Suspension/Drops	Ophthalmic	Prescription	Approved prior to 01/01/1982

Abbreviation: ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

Table 4. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Prednisolone acetate	0.12, 1%	Eye drops, Solution, Suspension	Ocular, Ophthalmic	Abu Dhabi	Active	–
				Canada	Prescription	12/31/1974
				Hong Kong	Prescription only medicine	06/04/1983
				New Zealand	Prescription	07/10/1975
				Saudi Arabia	Prescription	–
	0.12%	Eye drops, Suspension	Ophthalmic	Ireland	Prescription-only renewable	04/01/1977
	1%	Eye drops, Solution, Suspension	Ocular use, Ophthalmic	Belgium	Medical prescription	04/13/1988
				Ireland	Prescription-only non-renewable	04/01/1977
				Namibia	–	12/23/1976
				UK	Prescription-only medication	03/03/1988

Abbreviations: "–", not mentioned; ROA, route of administration.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Summary of literature review

No literature review was conducted.

Table 5. Types of studies

No literature review was conducted

Table 6. Number of studies by country

No literature review was conducted

Table 7. Number of studies by combinations

No literature review was conducted

Table 8. Dosage by indication – US

No literature review was conducted

Table 9. Dosage by indication – non-US countries

No literature review was conducted

Table 10. Compounded products – US

No literature review was conducted

Table 11. Compounded products – non-US countries

No literature review was conducted

Summary of focus groups/interviews of medical experts and specialty organizations

One (1) interview was conducted.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Prednisolone acetate	Interview Summary Response
OPH_05	MD	Ophthalmology/ Retina specialist	Academic medical institution	Yes	• Stated that the only reason they would want to get it from a compounding pharmacy is cost/

Abbreviation: MD, Doctor of Medicine.

Use of prednisolone acetate

- One (1) interviewee stated that the commercial prednisolone acetate is used for uveitis, which is "an inflammation in the eye that can occur for lots of different reasons."

Compounding prednisolone acetate

- One (1) interview stated that the benefit for compounding prednisolone acetate would be "cost marketing."
    - "So, people have cataract surgery. I could see this being a thing. People have cataract surgery and post-op, patients are given a steroid and an antibiotic to use. And if you could make it all in a package, and give it out from the surgery center, that probably would be convenient. But I don't think it's necessary. It's probably a marketing type thing."

Summary of survey results

Table 13. Characteristics of survey respondents [102 people responded to the survey[a]]

Board Certification	MD	No Response
Internal Medicine	2	0
Ophthalmology	59	0
No Board Certification	1	0
No Response	0	42

Abbreviation: MD, Doctor of Medicine.
[a]Some respondents reported more than one (1) board certification.

Table 14. Types of products used, prescribed, or recommended

Types of Products	Respondents, n (N=92[a])
Compounded	7[b]
FDA-approved	56
Over-the-counter	1
Dietary	0
Unsure	2
No Response	33

[a]Out of 102 respondents, 92 reported using, prescribing, or recommending multiple types of prednisolone acetate product.
[b]Two (2) respondents used in combination (see Figure 2).

Figure 2. Compounded combinations reported in the survey

- Prednisolone acetate, dilating drops
- Prednisolone acetate, Durezol (difluprednate)
- "'Lessdrops' from imprimis"[a]

[a]ImprimisRx® is a compounding pharmacy that formulates LessDrops®, a line of combination topical drop products. LessDrops products include the following combinations: prednisolone acetate, gatifloxacin; prednisolone acetate, bromfenac; prednisolone acetate, gatifloxacin, bromfenac.

Table 15. Compounded use of prednisolone acetate in practice[a]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Allergy to preservatives, allergic to BAK	1%	Any	Topical	Topical	Days to weeks	Allergic to BAK
Cataract surgery perioperative drops[b]	1%	Three times per day	Drop	Topical	2 weeks	Cataract patients
Corneal transplant protection	–	As needed according to clinical situation	Ocular drops	Ocular drops	As long as needed	Adults and children
Macular edema	1%	–	Drop	Ocular	–	–
Ocular inflammation	–	As needed according to clinical situation	Ocular drops	Ocular drops	As long as needed	Adults and children
Post-operative care	1%	Four times per day	Drop	Ocular	1 month	–
Uveitis	1%	Two to ten times per day	Drop	Ocular	1 week to chronic	–

Abbreviations: "–", not mentioned; BAK, benzalkonium chloride; ROA, route of administration.
[a]Six (6) respondents.
[b]Used in combination with other medications.

Table 16. Indications for which prednisolone acetate is considered a standard therapy[a]

Indication	Standard Therapy			
	Compounded, n (N=7)	Non-compounded, n (N=50)	Unsure, n (N=2)	No Response, n (N=33)
Allergies, severe	1	0	0	0
Corneal opacities	1	0	0	0
Dry eye, Ocular surface disease	0	2	0	0
Hyphema	1	0	0	0
Intraocular inflammation[b]	4	44	2	0
Irvine-Gass syndrome	0	1	0	0
Macula edema	1	1	0	0
Other[c]	2	0	0	0
Post-operative procedure[d]	1	30	0	0
Viral corneal disease	0	1	0	0
No Response	1	3	0	33

[a]Some respondents reported more than one indication.
[b]Ocular inflammatory conditions include: allergic conjunctivitis, anterior uveitis, blepharoconjunctivitis, conjunctivitis, Du pixent-associated conjunctivitis, episcleritis, iritis, keratitis, primary iridocyclitis, scleritis, uveitis.
[c]"Patient to need ongoing steroid therapy and preservative-free therapy;" "inflammation in patient with preservative allergy or corneal toxicity."
[d]Post-operative procedures include: cataracts, cornea transplant, ocular surgery, perioperative, penetrating keratoplasty (PK), transplant rejection.

Table 17. Reasons for using compounded product instead of the FDA-approved products

Theme	Reasons
Availability	Preservative-free • "Need preservative-free product" • "Preservatives" • "No BAK/preservative free alternative"
	"Availability as a compounded product"
	"Frequently on back order"
Cost	Cost of treatment • "Price to patient" • "Excessively expensive"
Prescriptive authority	"Further, it is not the FDA's role to tell me how to take care of patients"

Table 18. Change in frequency of compounded prednisolone acetate usage over the past 5 years

	Respondents, n (N=7)
No–use has remained consistent	4
Yes–I use it LESS often now	0
Yes–I use it MORE often now[a]	2
No Response	1

[a]One (1) respondent wrote "Availability of combination drops for patient compliance inconvenience, as well as variable and sometimes excessive cost or inability to obtain generic medication."

Table 19. Do you stock non-patient specific compounded prednisolone acetate in your practice?

	Respondents, n (N=7)
No	4
Yes	2
No Response	1

Table 20. Questions related to stocking non-patient specific compounded prednisolone acetate

	Respondents, n (N=2)
In what practice locations do you stock non-patient-specific compounded prednisolone acetate?	
Physician office	2
Outpatient clinic	0
Emergency room	0
Operating room	0
Inpatient ward	0
How do you obtain your stock of non-patient-specific compounded prednisolone acetate?	
Purchase from a compounding pharmacy	1
Purchase from an outsourcing facility	1
Compound the product yourself	0
Why do you keep a stock of non-patient-specific compounded prednisolone acetate?[a]	
Convenience	1
Emergencies	0
Other (Preoperative consultation)	1
Other (Back order)	1

[a]Some respondents reported more than one reason for stocking non-patient-specific prednisolone acetate.

CONCLUSION

Prednisolone acetate (UNII code: 8B2807733D) was nominated for inclusion on the 503B Bulks List for use as an ophthalmic suspension to manage symptoms associated with acute anterior uveitis. Prednisolone acetate is available as an ophthalmic suspension in the US, as well as in Abu Dhabi, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK. There is a current USP monograph for prednisolone acetate.

No literature review was conducted for prednisolone acetate because the desired compounded product does not substantially differ from the commercially available, FDA-approved product.

The interviewee reported using prednisolone acetate in their practice but stated that the only reason they would want to obtain it from a compounding pharmacy would be for cost.

From the survey, 92 out of 102 respondents reported using, prescribing, or recommending prednisolone acetate, of which seven (7) of which reported using compounded products. Two (2) reported using compounded prednisolone acetate as combination products. The most common indications respondents used compounded and non-compounded prednisolone acetate were for intraocular inflammation and post-operative procedures. Reasons for using the compounded prednisolone acetate products over an FDA-approved product could be categorized as availability, cost, and prescriptive authority. Out of the seven (7) respondents who reported using compounded prednisolone acetate, four (4) stated that use has remained consistent over the past 5 years and two (2) said they use it more often now. Two (2) respondents said they stock non-patient-specific compounded prednisolone in their physician office; one (1) purchases their stock from a compounding pharmacy and one (1) from an outsourcing facility. Reasons for stocking non-patient specific compounded prednisolone acetate were convenience, ensuring the patient gets the right product at the time of their preoperative consultation, and only when the product is not available in pharmacies due to manufacturer backorder.

APPENDICES

Appendix 1. References

No literature review was conducted.

Appendix 2. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **prednisolone acetate**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Prednisolone acetate

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **prednisolone acetate**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for prednisolone acetate? Please check all th... != Compounded drug product

Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for prednisolone acetate? Please check all th... = Compounded drug product

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Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for prednisolone acetate? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **prednisolone acetate** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **prednisolone acetate** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q5 If Do you use compounded prednisolone acetate as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded prednisolone acetate as a single agent active ingredient, or as one active ingredient... = Combination

Q4. Please list all combination products in which you use compounded **prednisolone acetate**.

_____

Q5. For which, if any, diseases or conditions do you consider compounded **prednisolone acetate** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **prednisolone acetate** in medical practice guidelines or other resources?

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **prednisolone acetate** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why) _____
- ○ Yes - I use it **LESS** often now (briefly describe why) _____
- ○ No - use has remained consistent

Q8. Why do you use compounded **prednisolone acetate** instead of any FDA-approved drug product?

_____

Q9. Do you stock non-patient-specific compounded **prednisolone acetate** in your practice location?

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded prednisolone acetate in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded prednisolone acetate in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **prednisolone acetate**? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **prednisolone acetate**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **prednisolone acetate**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded prednisolone acetate? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded prednisolone acetate? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded prednisolone acetate? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **prednisolone acetate** standard therapy?

_____

Q14. Does your specialty describe the use of **prednisolone acetate** in medical practice guidelines or other resources?

_____

End of Block: Prednisolone acetate

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ☐ Doctor of Medicine (MD)
- ☐ Doctor of Osteopathic Medicine (DO)
- ☐ Doctor of Medicine in Dentistry (DMD/DDS)
- ☐ Naturopathic Doctor (ND)
- ☐ Nurse Practitioner (NP)
- ☐ Physician Assistant (PA)
- ☐ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ☐ No Board certification
- ☐ Allergy and Immunology
- ☐ Anesthesiology
- ☐ Cardiovascular Disease
- ☐ Critical Care Medicine
- ☐ Dermatology
- ☐ Emergency Medicine
- ☐ Endocrinology, Diabetes and Metabolism
- ☐ Family Medicine
- ☐ Gastroenterology
- ☐ Hematology
- ☐ Infectious Disease
- ☐ Internal Medicine
- ☐ Medical Toxicology
- ☐ Naturopathic Doctor
- ☐ Naturopathic Physician
- ☐ Nephrology
- ☐ Neurology
- ☐ Obstetrics and Gynecology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Otolaryngology
- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe) _____

End of Block: Background Information