

Summary Report

Triamcinolone

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

Triamcinolone (UNII code: 1ZK20VI6TY) was nominated for inclusion on the 503B Bulks List by David Smith. While the exact medical condition for which the compounded product is being requested may be unknown, triamcinolone is generally indicated for a variety of skin conditions including eczema, dermatitis, allergies, and rash. Triamcinolone will be compounded into a topical cream at a strength that is based on the prescriber's request in combination with other active pharmaceutical ingredients (API), refer to Table 7 for the nominated combination formulations.

Reasons provided for nomination to the 503B Bulks List include:

- There is no FDA-approved drug product which combines triamcinolone with either hydroquinone or hydrocortisone, tretinoin, and glycolic acid in a topical form.
- When requested by physician after determining that there is a clinical difference between the compounded drug that is being requested and the commercially available drug products.
- Compounding from bulk allows for the inclusion of only the ingredients that are necessary to achieve the desired clinical outcome.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of triamcinolone 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 triamcinolone; name variations of triamcinolone 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 triamcinolone. 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

Search strategy

Two databases (PubMed and Embase) were searched including any date through March 28, 2019. The search included a combination of (triamcinolone[TIAB] AND (cream OR topical*) AND (hydroquinone OR hydrocortisone OR tretinoin OR "retinoic acid" OR "glycolic acid") AND (treat*[TIAB] OR therap*[TIAB] OR clinic*[TIAB] OR "skin"[TIAB] OR derm*[TIAB] OR eczema*[TIAB] OR allerg*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Triamcinolone is a component of an FDA-approved product that has been discontinued by the manufacturer, not for safety or efficacy reasons. As a result, articles were excluded if triamcinolone was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of triamcinolone or the implementation of triamcinolone in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

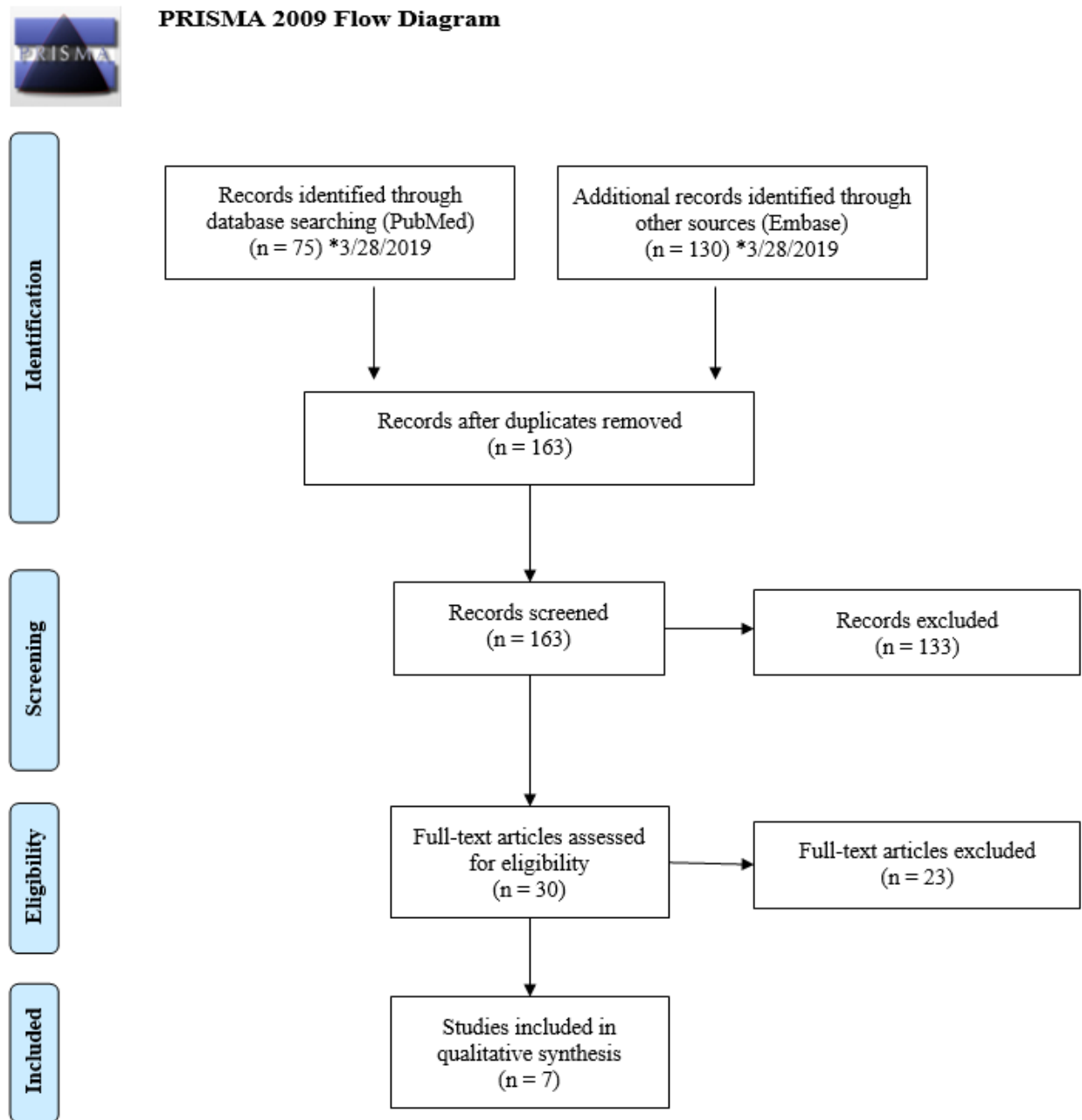
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for triamcinolone use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of triamcinolone compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nomination and the results of the literature review, three (3) medical specialties that would potentially use triamcinolone were identified: dermatology, primary care, and surgery. Semi-structured interviews were conducted with subject matter experts within these specialties. 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 interviews, of which once (1) accepted and zero (0) declined interviews. 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 dermatology, primary care, and surgery, identified from the nomination, literature review, 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 eight (8) 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
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Primary Care	American Academy of Environmental Medicine (AAEM)

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
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Surgery	American College of Surgeons (ACS)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Triamcinolone is not currently available as an FDA-approved product. Triamcinolone is available in various dosage forms as a single-agent topical product as the acetonide salt form.
- Triamcinolone is not available as an OTC product in the US in the nominated form.
- There is a current United States Pharmacopoeia (USP) monograph for triamcinolone.
- Triamcinolone is not approved in any of the foreign medicine registries searched. In Abu Dhabi and Latvia, triamcinolone is available in dosage forms that differ from those nominated.

Table 3. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and regions

Summary of literature review

- Total number of studies included: seven (7) studies (7 descriptive).
- Most of the studies were from the US (7).
- The most common indication for the use of triamcinolone in the US was graft-vs-host disease. The most common indication from the non-US studies was lichen planus.
- No compounded products were identified from any studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive ¹⁻⁷	7
Experimental	0
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
The Netherlands ⁷	1
United States (US) ¹⁻⁶	6
Total US: 6 Total Non-US Countries: 1	

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Triamcinolone / Glycolic acid/ Hydrocortisone/ Tretinoin - topical cream	0
	Triamcinolone / Glycolic acid/ Hydroquinone/ Tretinoin - topical cream	0
Others found in literature	Triamcinolone / Tretinoin <ul style="list-style-type: none"> • 0.1% cream⁶ • 0.1% / 0.025% - topical⁷ 	2

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Graft-vs-host disease ^{2,5}	–	0.1-1%	Cream	Topical	1 month
Exfoliative erythroderma flare ⁴	–	0.1%	Cream	Topical	–
Porokeratotic eccrine ostial duct nevus ⁶	–	0.1%	Cream	–	–
Postinflammatory Hyperpigmentation ³	–	0.1%	Cream	Topical	4 months
Pruritus ¹	–	–	Cream	Topical	–

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Lichen planus ⁷	–	0.1%	–	Topical	–

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

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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 Triamcinolone	Interview Summary Response
DER_06	MD	Dermatology/Immunology	Independent Consultant	Not mentioned	<ul style="list-style-type: none">• No need for use in office

Abbreviation: MD, Doctor of Medicine.

Use as a combination product

- The interviewee stated that the nominators might be compounding a modified Kligmans’ formula, which original included hydrocortisone, hydroquinone and a retinoid, which was used to treat melasma, sun-spots, post-inflammatory pigment changes, and as a fade cream. Some formulations use various alpha/beta hydroxyl acids, like glycolic acid.
- Triamcinolone is more potent than hydrocortisone.
- The interviewee stated that they personally do not want fluorinated steroids on the face continuing that non-fluorinated steroids are generally safer for use on thin-skinned areas, like the face.

Summary of survey results

Table 13. Characteristics of survey respondents [4 people responded to survey^a]

Board Certification	MD	PhD
Dermatology	3	0
Pediatric dermatology	1	0
No Board certification	0	1

Abbreviations: MD, Doctor of Medicine; PhD, Doctor of Philosophy.

^aSome respondents reported more than one terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=2^a)
Compounded	1 ^b
FDA-approved	2
Over-the-counter	0
Dietary	0
Unsure	0
No response	0

^aOut of four (4) respondents, two (2) reported using, prescribing, or recommending multiple types of triamcinolone product.

^bOne (1) respondent used in combination: “tmc plus lidocaine”.

Table 15. Compounded use of triamcinolone in practice^a

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Alopecia areata	5mg	Once a month	Diluted with lidocaine	Intralesional	As needed	Over 9
Granuloma annulare, hypertrophic lichen planus, psoriasis, prurigo nodularis						Over 15
Hypertrophic scars, keloids	3-5mg		–		1-3 times	Over 14

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

^aOne respondent.

Table 16. Indications for which triamcinolone is considered a standard therapy

Indication ^a	Standard Therapy	
	Compounded, n (N=1)	Non-compounded, n (N=1)
Cystic acne, granuloma annulare, hypertrophic lichen planus, prurigo nodularis	1	0
Eczema, seborrheic dermatitis	0	1
Psoriasis	1	1

^aSome respondents reported more than one indication

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

Reasons
“The current products are too concentrated and are likely to cause a trophy undiluted”

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

	Respondents, n (N=1)
No—use has remained consistent	1
Yes—I use it LESS often now	0
Yes—I use it MORE often now	0

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

	Respondents, n (N=1)
No	1
Yes	0

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

No survey respondents provided this information

CONCLUSION

Triamcinolone (UNII code: 1ZK20VI6TY) was nominated for inclusion on the 503B Bulks List by David Smith. While the exact medical condition for which the compounded product is being requested may be unknown, triamcinolone is generally indicated for a variety of skin conditions including eczema, dermatitis, allergies, and rash. Triamcinolone will be compounded into a topical cream at a strength that is based on the prescriber's request in combination with other active pharmaceutical ingredients (API). Triamcinolone is not approved in any of the foreign medicine registries searched. Triamcinolone acetonide is FDA-approved in the US in various topical dosage forms.

From the literature review conducted, the most common indication for the use of triamcinolone in the US was graft-vs-host disease. The most common indications from the non-US studies was lichen planus. No compounded products were identified from any studies.

The interviewee stated there is no need for use of triamcinolone in the office.

From the survey responses, two (2) out of four (4) respondents used triamcinolone; one (1) of these respondents used the compounded product. Compounded triamcinolone was reported for the use of alopecia areata, granuloma annulare, hypertrophic lichen planus, hypertrophic scars, keloids, psoriasis, and prurigo nodularis. The respondent reported using compounded triamcinolone because the commercially available product is too concentrated and risks causing atrophy if not diluted. The respondent did not report stocking compounded triamcinolone as office stock.

APPENDICES

Appendix 1. References

1. Anderson E, Rhatican J, Livesey C, Stinnett J. Suicidal ideation triggered by intractable lichen in Sézary syndrome: A clinical case study. *Psychooncology*. 2015;24(Suppl 2):300.
2. Chen T, Khan SP, Rodriguez V, Tollefson M. Use of NB-UVB phototherapy in pediatric graft-versus-host disease patients. *Biol Blood Marrow Transplant*. 2016;22(3):S391.
3. Hasan AT, Eaglstein W, Pardo RJ. Solar-induced postinflammatory hyperpigmentation after laser hair removal. *Dermatol Surg*. 1999;25(2):113-115.
4. Loukas E. High-Output heart failure in a patient with exfoliative erythroderma psoriasis. *J Hosp Med*. 2010;5(Suppl 1):162-163.
5. Sharp H, Grosshans D, Kadia T, Dabaja BS. Cutaneous graft-versus-host disease after proton-based craniospinal irradiation for recurrent Philadelphia-positive acute lymphoblastic leukaemia. *BMJ Case Rep*. 2012;2:1-6.
6. Smith J, Funk T, Leitenberger S, Krol A. Systematized porokeratotic eccrine ostial and dermal duct nevus (PEODDN) with good clinical and symptomatic response to topical tazarotene therapy. *Pediatr Dermatol*. 2017;34(Suppl 1):S59.
7. van Tuyll van Serooskerken A-M, van Marion AMW, de Zwart-Storm E, Frank J, Poblete-Gutiérrez P. Lichen planus with bullous manifestation on the lip. *Int J Dermatol*. 2007;46(Suppl 3):25-26.

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 **triamcinolone**. 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: Triamcinolone

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **triamcinolone**? 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 triamcinolone? Please check all th... != Compounded drug product

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

Display This Question:

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

Q2. Please list any conditions or diseases for which you use compounded **triamcinolone** 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 **triamcinolone** 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 triamcinolone as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

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

Q4. In which combination(s) do you use compounded **triamcinolone**? Please check all that apply.

- Triamcinolone / Glycolic Acid / Hydrocortisone / Tretinoin
- Triamcinolone / Glycolic Acid / Hydroquinone / Tretinoin
- Other (please describe) _____

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

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

Q7. Over the past 5 years, has the frequency in which you have used compounded **triamcinolone** 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 **triamcinolone** instead of any FDA-approved drug product?

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

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

End of Block: Triamcinolone

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