

Summary Report

Ascorbyl Palmitate

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

Ascorbyl palmitate (UNII code: QN83US2B0N) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC for melasma, bruising, and hyperpigmentation via a 1-2% topical formulation; the specific dosage forms were not included. The nominator identified the need to compound ascorbyl palmitate in combination with other active pharmaceutical ingredients (API) for a synergistic effect; however, the additional APIs were not specified.

The reasons provided for nomination to the 503B Bulks List were that there is no FDA-approved product commercially available and the need to compound ascorbyl palmitate in combination with other APIs.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ascorbyl palmitate 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 (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 ascorbyl palmitate; name variations of ascorbyl palmitate 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(s); 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 ascorbyl palmitate. 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 December 10, 2018. The search included a combination of (asc6Plm [TIAB] OR "ascorbic palmitate"[TIAB] OR "ascorbyl palmitate"[TIAB] OR "ascorbate 6-palmitate"[TIAB] OR "ascorbic acid-6-O-palmitate"[TIAB] OR "l-Ascorbyl 6-palmitate"[TIAB] OR "l-ascorbic acid 6-hexadecanoate"[TIAB] OR "6-O-palmitoylascorbate"[TIAB] OR "6-o-palmitoylascorbic acid"[TIAB] OR "6-O-Palmitoyl-L-ascorbic acid"[TIAB] OR "vitamin C-palmitate"[TIAB]) AND (treatment OR therapy OR therapeutic OR clinical OR dermatology OR skin) 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. Articles were considered relevant based on the identification of a clinical use of ascorbyl palmitate or the implementation of ascorbyl palmitate 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.

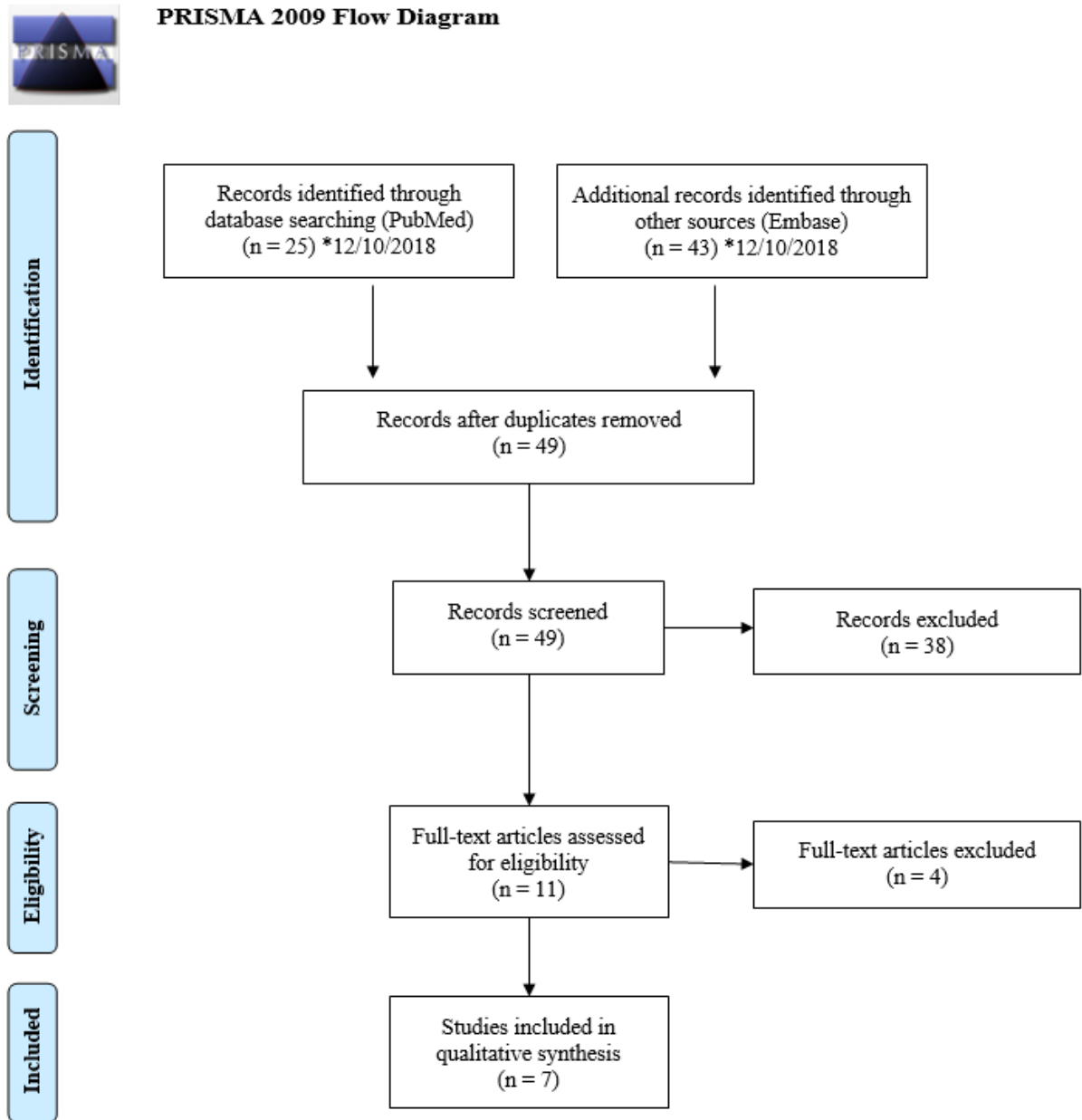
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for ascorbyl palmitate 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 ascorbyl palmitate 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 ascorbyl palmitate were identified: dermatology, endocrinology, and naturopathy. 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. Two (2) experts were contacted for interviews, of which two (2) accepted and zero (0) declined interviews. The interviews were 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, endocrinology, and naturopathy, identified from the nominations, literature review, and interviews, 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 six (6) 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) |
| Naturopathy | American Association of Naturopathic Physicians (AANP) |

Table 2. Associations that declined participation

| Specialty | Association | Reasons for Declining |
|------------------|--|---|
| Endocrinology | American Association of Clinical Endocrinologists (AACE) | Declined, “endocrinologists are not generally in the compounding space” |
| Medicine | American Medical Association (AMA) | Failed to respond |
| | American Osteopathic Association (AOA) | Failed to respond |

CURRENT AND HISTORIC USE

Summary of background information

- Ascorbyl palmitate is not available as an FDA-approved product.
- Ascorbyl palmitate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for ascorbyl palmitate.
- Ascorbyl palmitate is not available in any of the foreign medicine registries searched.

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: 7 studies (2 descriptive and 5 experimental).
- Most of the studies were from Pakistan (3).
- One (1) US study was identified with an indication for hyperpigmentation. From the non-US studies, the most common indication was erythema. There was also one (1) non-US study that discussed use in hyperpigmentation.
- For the US study, no compounded products were identified. From the non-US studies, there were four (4) studies that discussed use as a compounded product (0.5-1% emulsion and 1% gel).

Table 5. Types of studies

| Types of Studies | Number of Studies |
|-----------------------------|--------------------------|
| Descriptive ^{1,2} | 2 |
| Experimental ³⁻⁷ | 5 |
| Observational | 0 |

Table 6. Number of studies by country

| Country | Number of Studies |
|--|--------------------------|
| Canada ² | 1 |
| France ⁷ | 1 |
| Italy ⁶ | 1 |
| Pakistan ³⁻⁵ | 3 |
| US ¹ | 1 |
| Total US: 1 Total non-US Countries: 6 | |

Table 7. Number of studies by combinations

The nomination identified the need for combination products, however, no information was provided regarding the specific combinations desired.

Table 8. Dosage by indication – US

| Indication | Dose | Concentration | Dosage Form | ROA | Duration of Treatment |
|--------------------------------|-------------|---------------|-------------|---------|-----------------------|
| Hyperpigmentation ¹ | 10mg/kg/day | – | – | Topical | 12 weeks |

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

Table 9. Dosage by indication – non-US countries

| Indication | Dose | Concentration | Dosage Form | ROA | Duration of Treatment |
|--|--------|---------------|---------------|---------|-----------------------|
| Erythema ^{5,6} | – | 0.5% | Emulsion | Topical | 12 weeks |
| | – | 1% | Emulsion, gel | | Twice |
| Diabetic peripheral neuropathy ⁷ | – | – | Cream | Topical | 4 weeks |
| Facial sebum control ⁴ | – | 0.5% | Emulsion | Topical | 12 weeks |
| Fortifying facial skin collagen ³ | 2g/day | 0.5% | Emulsion | Topical | 12 weeks |
| Hyperpigmentation ² | – | – | Cream | Topical | 12 weeks |

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

| Indication | Compounding Method | Dosage Form | Final Strength | | | | |
|--|--|--|--|--|--|----------|----|
| Erythema ^{5,6} | <p>Two-step emulsification procedure – primary emulsion: prepared by emulsifying the oil phase with the aqueous phase in the presence of lipophilic surfactant. Both phases were preheated to 75°C in a digital water bath before mixing. Mixing of W/O emulsion components was done using IKA Mixing Overhead Stirrer at 2000 rpm to obtain small inner droplets. Secondary emulsification: emulsion dispersed in external aqueous phase containing hydrophilic emulsifier. Mixed at 700 rpm x 40 min.⁵</p> <table border="0" style="width: 100%;"> <tr> <td style="width: 33%; vertical-align: top;"> <p>Primary Emulsion 1</p> <ul style="list-style-type: none"> • CDC 2.4% • Liquid paraffin 13.6% • MgSO₄ 0.56% • Sodium ascorbyl palmitate 0.25% • Ascorbyl palmitate 0.5% • Deionized water 62.69% <p>Multiple Emulsion 1</p> <ul style="list-style-type: none"> • Polysorbate-80 0.8% • Sodium ascorbyl palmitate 0.25% • Water (q.s.) 100% </td> <td style="width: 33%; vertical-align: top;"> <p>Primary Emulsion 2</p> <ul style="list-style-type: none"> • CDC 2.4% • Liquid paraffin 13.6% • MgSO₄ 0.56% • Ascorbyl palmitate 0.5% • Deionized water 62.69% <p>Multiple Emulsion 2</p> <ul style="list-style-type: none"> • Polysorbate-80 0.8% • Sodium ascorbyl palmitate 0.5% • Water (q.s.) 100% </td> <td style="width: 33%; vertical-align: top;"> <p>Primary Emulsion 3</p> <ul style="list-style-type: none"> • CDC 2.4% • Liquid paraffin 13.6% • MgSO₄ 0.56% • Sodium ascorbyl palmitate 0.5% • Ascorbyl palmitate 0.5% • Deionized water 62.44% <p>Multiple Emulsion 3</p> <ul style="list-style-type: none"> • Polysorbate-80 0.8% • Water (q.s.) 100% </td> </tr> </table> | <p>Primary Emulsion 1</p> <ul style="list-style-type: none"> • CDC 2.4% • Liquid paraffin 13.6% • MgSO₄ 0.56% • Sodium ascorbyl palmitate 0.25% • Ascorbyl palmitate 0.5% • Deionized water 62.69% <p>Multiple Emulsion 1</p> <ul style="list-style-type: none"> • Polysorbate-80 0.8% • Sodium ascorbyl palmitate 0.25% • Water (q.s.) 100% | <p>Primary Emulsion 2</p> <ul style="list-style-type: none"> • CDC 2.4% • Liquid paraffin 13.6% • MgSO₄ 0.56% • Ascorbyl palmitate 0.5% • Deionized water 62.69% <p>Multiple Emulsion 2</p> <ul style="list-style-type: none"> • Polysorbate-80 0.8% • Sodium ascorbyl palmitate 0.5% • Water (q.s.) 100% | <p>Primary Emulsion 3</p> <ul style="list-style-type: none"> • CDC 2.4% • Liquid paraffin 13.6% • MgSO₄ 0.56% • Sodium ascorbyl palmitate 0.5% • Ascorbyl palmitate 0.5% • Deionized water 62.44% <p>Multiple Emulsion 3</p> <ul style="list-style-type: none"> • Polysorbate-80 0.8% • Water (q.s.) 100% | Emulsion | 0.5% | |
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| | <p>Emulsion: Phase A was heated to 75°C; phase B was heated to 75°C under vacuum mixing with a turbomixer and paddles. Phase B was added to phase A and mixed; then cooled to 40°C and phase C was added. The formulation was cooled to room temperature, with continued mixing. Then active components added.⁶</p> <table border="0" style="width: 100%;"> <tr> <td style="width: 33%; vertical-align: top;"> <p>Phase A</p> <ul style="list-style-type: none"> • Sucrose distearate 5% • Petrolatum/lanolin alcohol 1% • Cyclomethicone/PPG-15 stearyl ether 1.5% • Dioctyl adipate 9% • Cethyl alcohol 1% • Sweet almond oil 3% • Shea butter 3.5% • Phenosyethanol 0.8% • Butylhydroxyanisol 0.05% </td> <td style="width: 16.5%; vertical-align: top;"> <p>Phase B</p> <ul style="list-style-type: none"> • Xanthan gum 0.2% • Disodium EDTA 0.2% • Glycerin 4% • Water 70.5% </td> <td style="width: 16.5%; vertical-align: top;"> <p>Phase C</p> <ul style="list-style-type: none"> • Imidazolindinyl urea 0.25% </td> <td style="width: 34%; vertical-align: top;"> <p>Active Components</p> <ul style="list-style-type: none"> • Ascorbyl palmitate 1% </td> </tr> </table> | <p>Phase A</p> <ul style="list-style-type: none"> • Sucrose distearate 5% • Petrolatum/lanolin alcohol 1% • Cyclomethicone/PPG-15 stearyl ether 1.5% • Dioctyl adipate 9% • Cethyl alcohol 1% • Sweet almond oil 3% • Shea butter 3.5% • Phenosyethanol 0.8% • Butylhydroxyanisol 0.05% | <p>Phase B</p> <ul style="list-style-type: none"> • Xanthan gum 0.2% • Disodium EDTA 0.2% • Glycerin 4% • Water 70.5% | <p>Phase C</p> <ul style="list-style-type: none"> • Imidazolindinyl urea 0.25% | <p>Active Components</p> <ul style="list-style-type: none"> • Ascorbyl palmitate 1% | Emulsion | 1% |
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| | | | | | | | |
|--|--|--|---|---|--|-----|----|
| | <p>Gel: Base gel – phase A was heated to 50°C under vacuum mixing with a turbomixer and paddles. Phase B was heated to 50°C until complete solubilization of butylhydroxyanisol. Phase B was added to phase A by stirring, and then C was added. Mixing was continued and the mixture cooled down to room temperature. Then active components added.⁶</p> | | | | | | |
| | <table border="0"> <tr> <td style="vertical-align: top;"> <p>Phase A</p> <ul style="list-style-type: none"> • Water 91.5% • Acrylates/C 10-30 alky acrylate crosspolymer 0.6% • Glycerin 5% • Disodium EDTA 0.1% • Diazolidinyl urea 0.25% </td> <td style="vertical-align: top; padding-left: 20px;"> <p>Phase B</p> <ul style="list-style-type: none"> • Phenoxyethanol 1% • Butylhydroxyanisol 0.05% </td> <td style="vertical-align: top; padding-left: 20px;"> <p>Phase C</p> <ul style="list-style-type: none"> • Sodium hydroxide (sol. 10%) 1.5% </td> <td style="vertical-align: top; padding-left: 20px;"> <p>Active Components</p> <ul style="list-style-type: none"> • Ascorbyl palmitate 1% </td> </tr> </table> | <p>Phase A</p> <ul style="list-style-type: none"> • Water 91.5% • Acrylates/C 10-30 alky acrylate crosspolymer 0.6% • Glycerin 5% • Disodium EDTA 0.1% • Diazolidinyl urea 0.25% | <p>Phase B</p> <ul style="list-style-type: none"> • Phenoxyethanol 1% • Butylhydroxyanisol 0.05% | <p>Phase C</p> <ul style="list-style-type: none"> • Sodium hydroxide (sol. 10%) 1.5% | <p>Active Components</p> <ul style="list-style-type: none"> • Ascorbyl palmitate 1% | Gel | 1% |
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| Fortifying facial skin collagen ³ | <p>Two-step emulsification procedure – primary emulsion was prepared by heating cetyl dimethicone copolyol, liquid paraffin, ascorbyl palmitate, water, and magnesium sulfate to 75°C in a digital water bath and then mixing by IKA Mixing Overhead Stirrer at 2000 rpm. Secondary emulsification – primary emulsion dispersed in mixture of water, polysorbate-80, and sodium ascorbyl palmitate at 700 rpm for 40 min.</p> | | | | | | |
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| Facial sebum control ⁴ | <p>Two-step emulsification procedure – primary emulsion was prepared by heating cetyl dimethicone copolyol, liquid paraffin, ascorbyl palmitate, water, and magnesium sulfate to 75°C in a digital water bath and then mixing by IKA Mixing Overhead Stirrer at 2000 rpm. Secondary emulsification – primary emulsion dispersed in mixture of water, polysorbate-80, and sodium ascorbyl palmitate at 700 rpm for 40 min.</p> | | | | | | |
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Summary of focus groups/interviews of medical experts and specialty organizations

Two (2) interviews were conducted.

Table 12. Overview of interviewees

| Interviewee | Level of Training | Specialty | Current Practice Setting | Experience with Ascorbyl Palmitate | Interview Summary Response |
|--------------------|--------------------------|--|---------------------------------|---|---|
| DER_04 | MD | Dermatology Dermatology/Immunology | Independent consultant | No | <ul style="list-style-type: none"> • No direct experience but very familiar with vitamin C products • Many products are available • Office stock not needed with some possible exceptions • Stability issues with vitamin C |
| END_02 | MD | Endocrinology, Diabetes and Metabolism | Academic medical institution | No | <ul style="list-style-type: none"> • Has never used this substance |

Abbreviation: MD, Doctor of Medicine.

Office stock:

- Many available products and options:
 - "...there's topical vitamin C products that are available, a lot of them. I don't know why somebody is getting bulk compounding done when you could go to the right place and get it."
- Possible exceptions:
 - "... why would somebody be needing that in their office, unless they are...there's a lot of dermatologists who do special cosmeceutical compounding."
 - Using it after a procedure.
- Issues with stability:
 - "Now whether it's stable or not is a bigger issue, and how long it's stable for. So they're dispensed in light-sensitive bottles, the brown amber bottles, and usually in relatively small amounts. Plus they can charge a lot more for it that way."

Compounding ascorbyl palmitate:

- “I’m struggling with the rationale for why you would need to have this as opposed to what else we have available that’s commercially there”
- One interviewee stated a possible reason could be challenges in its solubility.
 - “And that’s again the biggest problem with the vitamin C in general, is that they’re not stable. So there was a lot of magic that went into making the formulations to insure they could have a stable product.”

Summary of survey results

Table 13. Characteristics of survey respondents [8 people responded to the survey^a]

| Board Certification | MD | ND | No Response |
|----------------------------|-----------|-----------|--------------------|
| Naturopathic Doctor | 0 | 5 | 0 |
| Naturopathic Physician | 0 | 4 | 0 |
| No Board Certification | 0 | 0 | 0 |
| No Response | 0 | 0 | 2 |

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor.

^aSome respondents reported more than one (1) terminal clinical degree or board certification.

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

| Types of Products | Respondents, n (N=4^a) |
|--------------------------|---|
| Compounded | 2 |
| FDA-approved | 1 |
| OTC | 1 |
| Dietary | 2 |
| Unsure | 0 |
| No response | 0 |

^aOut of eight (8) respondents, four (4) reported using, prescribing, or recommending multiple types of ascorbyl palmitate product.

Table 15. Compounded use of ascorbyl palmitate in practice^a

| Indication | Strength | Dosing Frequency | Dosage Form | ROA | Duration of Treatment ^b | Patient Population ^b |
|------------|----------|------------------|-------------|-----|------------------------------------|---------------------------------|
| “Many bb” | – | – | – | – | – | – |

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

^aOne (1) respondent.

^bQuotations are direct words from respondents.

Table 16. Indications for which ascorbyl palmitate is considered a standard therapy

| Indication | Standard Therapy | |
|--------------------|---------------------|-------------------------|
| | Compounded, n (N=2) | Non-compounded, n (N=2) |
| Sun damage | 0 | 1 |
| Vitamin C support | 0 | 1 |
| Other ^a | 1 | 0 |
| No response | 1 | 0 |

^aQuote from respondent: “many !!”

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

| Reasons |
|---|
| <ul style="list-style-type: none"> • “better !!” |

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

| | Respondents, n (N=2) |
|--|----------------------|
| No–use has remained consistent | 0 |
| Yes–I use it LESS often now | 0 |
| Yes–I use it MORE often now ^a | 1 |
| No Response | 1 |

^aOne (1) respondent wrote “needed !!”

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

| | Respondents, n (N=2) |
|------------------|-----------------------------|
| No | 0 |
| Yes ^a | 1 |
| No Response | 1 |

^aOne (1) respondent reported stocking non-patient-specific compounded ascorbyl palmitate in the physician office and obtains product from a compounding pharmacy for the reason of convenience.

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

No additional survey respondents provided this information

CONCLUSION

Ascorbyl palmitate (UNII code: QN83US2B0N) was nominated for inclusion on the 503B Bulks List for melasma, bruising, and hyperpigmentation via a 1-2% topical formulation. The nominator identified the need to compound ascorbyl palmitate in combination with other active pharmaceutical ingredients (API) for a synergistic effect in treating each of these disease states; however, the additional API were not specified. Ascorbyl palmitate is not available in the US or any of the foreign medicine registries searched.

From the literature review, one (1) US study was identified with an indication for hyperpigmentation. From the non-US studies, the most common indication was erythema. There was also one (1) non-US study that used ascorbyl palmitate for hyperpigmentation. No compounded products were identified in the US study. From the non-US studies, four (4) studies discussed the use of compounded ascorbyl palmitate as a 0.5-1% emulsion and a 1% gel.

From the interviews conducted, one (1) interviewee had no experience with ascorbyl palmitate while the second interviewee expressed that there are many available products that the need for compounded ascorbyl palmitate is minimal. Additionally, office stock is usually not needed.

From the survey, four (4) out of eight (8) respondents reported using ascorbyl palmitate and two (2) of these respondents reported using a compounded product. One (1) respondent reported stocking non-patient-specific compounded ascorbyl palmitate in the physician office obtained via a compounding pharmacy for convenience.

APPENDICES

Appendix I. References

1. Draelos ZD. Hydroquinone: Optimizing therapeutic outcomes in the clinical setting of melanin-related hyperpigmentation. *Today's Ther Trends*. 2001;19(3):191-203.
2. Gupta AK, Ryder JE. Lustra , Lustra-AF and AlustraTM. *Skin Therapy Lett*. 2003;8(5):1-3.
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4. Khan H, Akhtar N, Ali A. Assessment of combined ascorbyl palmitate (AP) and sodium ascorbyl phosphate (SAP) on facial skin sebum control in female healthy volunteers. *Drug Res (Stuttg)*. 2017;67(1):52-58.
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6. Montenegro L, Bonina F, Rigano L, Giogilli S, Sirigu S. Protective effect evaluation of free radical scavengers on UVB induced human cutaneous erythema by skin reflectance spectrophotometry. *Int J Cosmet Sci*. 1995;17(3):91-103.
7. Valensi P, Le Devehat C, Richard JL, et al. A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy: A preliminary report. *J Diabetes Complications*. 2005;19(5):247-253.

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 **ascorbyl palmitate**. 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: Ascorbyl palmitate

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

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

Display This Question:

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

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

Display This Question:

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

Q4. Please list all combination products in which you use compounded **ascorbyl palmitate**.

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

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

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

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

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

End of Block: Ascorbyl palmitate

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