Summary Report

Urea

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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REVIEW OF NOMINATIONS

Urea (UNII code: 8W8T17847W) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC and the Outsourcing Facilities Association (OFA). While the exact medical condition for which the compounded drug is being requested is generally unknown, urea is generally used to promote rehydration of the skin. At higher concentrations urea is indicated for psoriasis, xerosis, onychomycosis, ichthyosis, eczema, keratosis, keratoderma, corns, and calluses. Urea was nominated for use as a topical product in dosage forms and strengths based on the prescriber's request; the therapeutic dose ranges 10-40%.

Urea was nominated for combination with other active pharmaceutical ingredients, refer to Table 7 for the nominated combination formulations.

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

- The dosage form, strength, or flavor of the commercially available product be not be appropriate for the patient.
- The commercially available product may contain excipients that cannot be tolerated by the patient due to sensitivities or allergies.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Patients respond differently to drug products and the compounded product may be the only formulation to effectively treat the indication for which it is intended to treat.
- There are no FDA-approved products containing urea commercially available.

METHODOLOGY

Background information

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

urea. 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 June 4, 2019. The search included a combination of (urea[TIAB] OR carbamide[TIAB]) AND (topical OR gel OR cream OR ointment OR solution OR suspension OR emulsion OR DMSO[TIAB] OR itraconazole[TIAB] OR ciclopirox[TIAB] OR ibuprofen[TIAB] OR tacrolimus[TIAB] OR "aloe vera"[TIAB] OR niacinamide[TIAB] OR "salicylic acid"[TIAB] OR "clobetasol propionate"[TIAB] OR "lactic acid"[TIAB]) AND (treat*[TIAB] OR therap*[TIAB] OR clinic*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism NOT (Review[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]). 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

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Urea is a component of an FDA-approved product, as a result, articles were excluded if urea 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 urea or the implementation of urea 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.

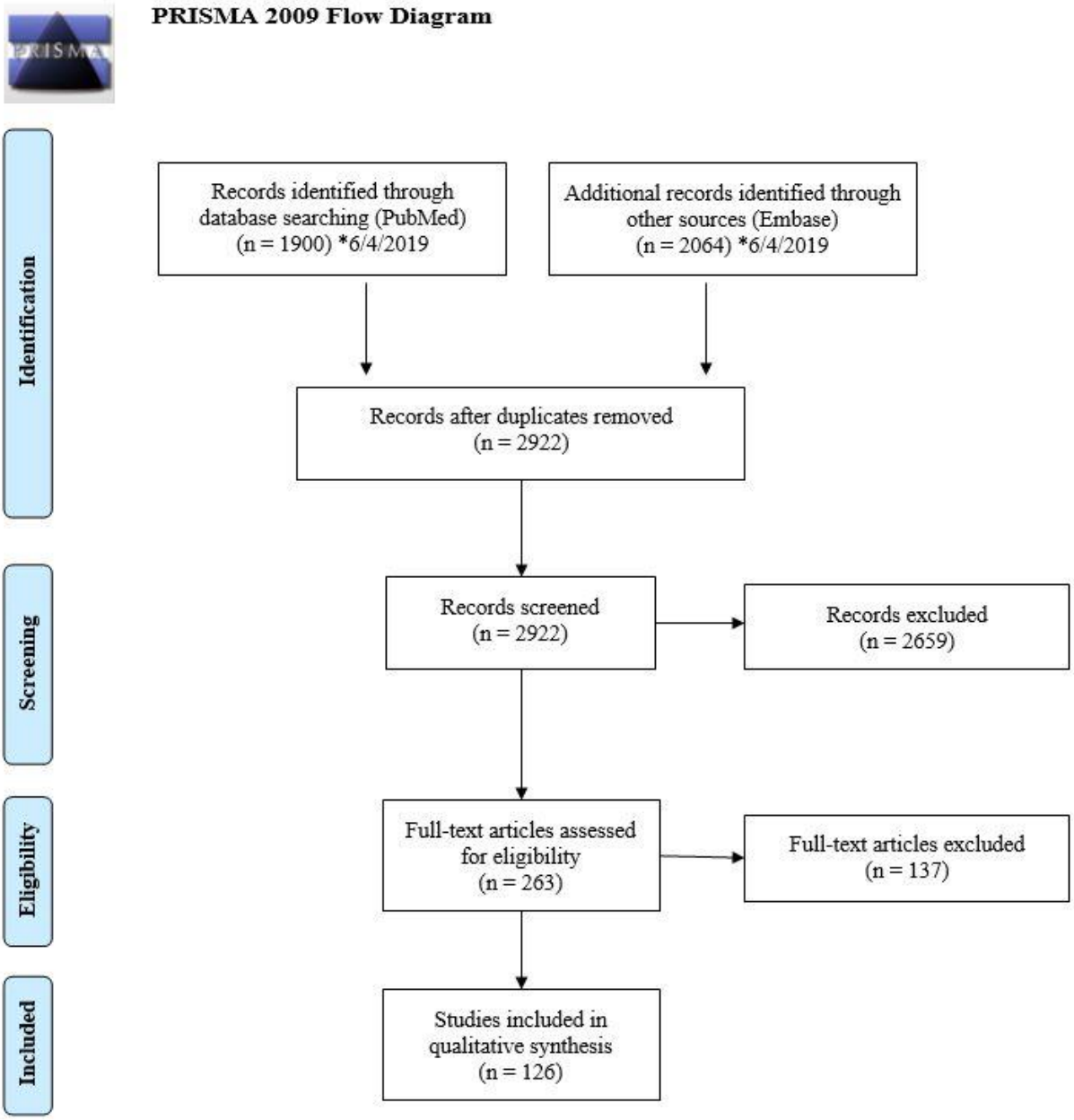
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for urea 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 urea 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). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: 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 nominations and the results of the literature review, one (1) medical specialty that would potentially use urea was identified: dermatology. 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 interviews, of which one (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, identified from the nominations and literature review, were contacted to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within the 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 four (4) 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)

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

- Urea is not available as an FDA-approved product.
- Urea is available in various topical dosage forms as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for urea.
- Urea is available in Abu Dhabi, Ireland, Namibia, and the UK (see Table 4).

Table 3. Currently approved products – US

No approved products in the US

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]
Urea	2%, 4%, 10%, 25%	Cream, Lotion, Ointment	Topical	Abu Dhabi	Active	–
				Ireland	Pharmacy-only[c]	01/29/1991
				Namibia	–	03/14/2005
				UK	Pharmacy	06/04/1991

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.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Summary of literature review

- Total number of studies included: 126 studies (47 descriptive, 48 experimental, and 31 observational).
- Most of the studies were from the US (30).
- The most common indications for the use of urea in the US were nail avulsion, warts, and hand-foot syndrome in patients taking capecitabine, sorafenib, or sunitinib. The most common indication from the non-US studies was onychomycosis.
- Compounded products were identified from both US and non-US studies that reflected the nominated indications in a topical dosage form.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-47]	47
Experimental[48-95]	48
Observational[96-126]	31

Table 6. Number of studies by country

Country	Number of Studies
Australia[3,41]	2
Belgium[113]	1
Brazil[57,65,106]	3
China[7,9,14,45,85,91,125]	7
Denmark[32,86]	2
Egypt[6]	1
Germany[17,25,35,67,68,78,79,107,117]	9
Hungary[108]	1
India[71,84,97]	3
Indonesia[77]	1
Iran[33,53,96]	3
Ireland[56]	1

Israel[48,123]	2
Italy[31,36,52,58,62,81,89,99,105,115,120]	11
Japan[11,92,111,126]	4
Mexico[4,28,29,47,49,54,55,61,116]	9
Poland[8,38]	2
Portugal[22,23]	2
Saudi Arabia[19]	1
Slovenia[100]	1
South Korea[10,51]	2
Spain[69,114,124]	3
Sweden[60,63,66,70,76,93]	6
Switzerland[21,122]	2
Thailand[102]	1
Turkey[16,24,26,98]	4
UK[13,37,43,94,101]	5
US[1,2,5,12,15,18,20,27,30,34,39,40,42,44,46,59,64,72-75,80,82,87,103,104,109,112,118,119]	30
Multiple Countries • France, Belgium, Italy, Poland[83] • Germany, Iceland, France[90] • Germany, UK, Switzerland[95] • Italy, Sweden[121] • UK, Germany[110] • US, Honduras, Switzerland[88] • US, Ecuador[50]	7
	Total US[a]: 32 Total non-US Countries[a]: 96

[a]Studies 50 and 88 counted in both US and non-US total.

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Urea 10% / Aloe Vera 0.2% / Fluocinolone acetonide 0.05% / Hyaluronic acid sodium salt 0.5% / Lactic acid 10%	0
	Urea 10% / Ciclopirox 2% / Ibuprofen 2% / Itraconazole 1% / Terbinafine HCl 4%	0
	Urea 20% / Clobetasol propionate 0.05% / Ibuprofen 2% / Mupirocin 5% / Salicylic acid 5%	0
	Urea 40% / Aloe Vera 0.5% / Hyaluronic acid sodium salt 0.5% / Salicylic acid 5%	0
	Urea 20% / Ciclopirox 3% / DMSO 5% / Itraconazole 5%	0
	Urea 40% / Aloe Vera 1% / Lactic acid 10%	0
	Urea 40% / Aloe Vera 1% / Niacinamide 4%	0
	Urea 40% / Clobetasol propionate 0.05% / Salicylic acid 4%	0
	Urea 20% / Hyaluronic acid sodium salt 1% / Tacrolimus 0.1%	0
Others found in literature	Urea / Chlorophyllin / Papain – topical ointment[1,80] • Urea 10% / Chlorophyllin 0.5% / Papain 10% – topical ointment[103]	3
	Urea 10% / Fluticasone 10% / Topical Retinoid 10% – topical[97]	1
	Urea 10% / Lactic acid 15% / Propylene glycol 50% – topical solution[63]	1
	Urea 20% / Niacinamide / Salicylic acid 2% – topical cream[81]	1
	Urea 10% / Aminosidine sulphate 12-15% – topical cream[101]	1
	Urea 20% / Ammonium lactate 12% – topical liquid soap[48]	1
	Urea 10% / Benzoyl peroxide 4.5 or 8.5% – topical gel, cream, cleanser[72]	1

	Urea 10% / Betamethasone valerate 0.1% – topical cream[110]	1
	Urea 40% / Bifonazole 1% – topical ointment[54,55,67,77,83,114,117,123], cream[95,124]	10
	Urea 20% / Butenafine HCL 2% – topical cream[94]	1
	Urea 20% / Clotrimazole – topical ointment[51]	1
	Urea 17% / Dithranol 0.1% – topical cream[56]	1
	Urea / Fluconazole • Urea 20% / Fluconazole 1% – topical liquid[99] • Urea 40% / Fluconazole 1% – topical liquid[53]	2
	Urea / 5-Fluorouracil – topical[4]	1
	Urea 20% / Hydrocortisone 0.5% – topical[93]	1
	Urea 35% / Lactic acid – topical foam[75]	1
	Urea 15% / 2,4,6-Octatrienoic acid 0.3% – topical[58]	1
	Urea 10% / Paromomycin 15% – topical ointment[50,88]	2
	Urea / Salicylic acid – topical[7] • Urea 10% / Salicylic acid – topical cream[3] • Urea 10% / Salicylic acid 5% – topical cream[33] • Urea 10-20% / Salicylic acid 10% – topical ointment[2,62,89]	6
	Urea 40% / Sodium chloride 40% – topical cream[76]	1
	Urea 25% / Sulfathiazole 75% – topical powder[30]	1
	Urea / Vitamin K1 0.1% – topical cream[36,115]	2

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Nail avulsion[2,39,64,119]	–	20, 22, 40%	Ointment	Topical	5 days-2 weeks
Warts[42,44,109,112]	–	40%	Cream, Gel	Topical	3 months-1 year
Hand-foot syndrome in patients receiving capecitabine[27], sorafenib[74,82], and sunitinib[82]	–	40%	Cream	Topical	6 weeks
Ulcers[87,103,118]	–	10%	Ointment, Solution	Topical	–
Cutaneous leishmaniasis[50,88]	–	10%	Ointment	Topical	4 weeks
Debridement[1,80]	–	–	Ointment	Topical	8 months
Pityriasis rubra pilaris[18,34]	–	–	–	Topical	–
Acne vulgaris[72]	–	10%	Cream	Topical	4 weeks
Aquagenic papulotranslucent acrokeratoderma[46]	–	–	Cream	Topical	–
Chronic tympanic membrane perforations[73]	–	40%	Ointment	Topical	–
Ecchymoses[20]	–	15%	Gel	Topical	8 hours
Ichthyosiform erythroderma[15]	–	–	Ointment	Topical	–
Impetigo[30]	–	25%	Powder	Topical	1 week
Keratoses[104]	–	40%	Cream	Topical	–
Moccasin tinea pedis[59]	–	40%	Cream	Topical	2-3 weeks
Necrolytic acral erythema[12]	–	–	Cream	Topical	–
Rash[5]	–	–	Cream	Topical	–

Tattoo removal[40]	–	–	–	Topical	–
Xerosis of the foot[75]	–	35%	Foam	Topical	4 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
Onychomycosis[21,23,25,31,49,51,53,54,60,61,63,67,69,77,83,90,94,95,99,102,108,114,116,117,120,121,124,125]	–	40%	Plaster, Cream	Topical	Once
	–	10-40%	Cream, Liquid, Ointment, Paste, Solution		4 days-18 months
Hand-foot syndrome in patients receiving capecitabine[68,78,126], regorafenib[111], and sorafenib[92]	–	10-20%	Cream, Ointment	Topical	6-7 weeks
Psoriasis[56,70,79,84]	–	10-17%	Cream, Gel	Topical	3-12 weeks
Skin toxicity associated with cetuximab[36,100,115,122]	–	–	Cream	Topical	–
Cutaneous leishmaniasis[50,88,101]	–	10%	Cream, Ointment	Topical	2-12 weeks
Radiation dermatitis[45,65,106]	–	–	Cream	Topical	Duration of radiotherapy
Warts[4,62,89]	–	10%	Ointment	Topical	Once
	–	20%	–		–
Atopic dermatitis[48,76]	–	20-40%	Cream, Liquid soap	Topical	2-3 weeks
Plaque psoriasis[66,81]	–	12-20%	Cream	Topical	7 days-4 weeks
Xerostomia[14,57]	–	10%	Ointment	Topical	3 months
Acne[71]	–	10%	Ointment	Topical	1 month

Actinic keratosis[107]	–	40%	Cream	Topical	Once
Aquagenic keratoderma[24]	–	10%	Lotion	Topical	–
Atopic eczema[110]	–	10%	Cream	Topical	10 days
Collagenous and elastotic marginal plaques of the hands[7]	–	–	–	Topical	–
Dermatitis plantaris sicca[113]	–	–	Cream	Topical	–
Epidermolytic hyperkeratosis[97]	–	10%	–	Topical	Indefinite
Focal acral hyperkeratosis[8]	–	20%	–	Topical	–
Harlequin ichthyosis[19]	–	–	Cream	Topical	–
Hyperkeratotic actinic keratosis[58]	–	15%	–	Topical	2 months
Hyperkeratotic type tinea pedis[91]	–	10%	Ointment	Topical	4 or 12 weeks
Ichthyosiform erythroderma[37]	–	15%	Cream	Topical	–
Keratitis-ichthyosis-deafness (KID) syndrome[96]	–	5, 10%	Cream	Topical	At least 2 weeks
Keratotic cap[41]	–	–	Cream	Topical	–
Large-cell acanthoma[16]	–	10%	Cream	Topical	1 month
Lichen planus[29]	–	20%	–	Topical	–
Lichen striatus[3]	–	10%	Cream	Topical	6 months
Lingua villosa nigra[13]	–	40%	Solution	Topical	–
Lipoid proteinosis[9]	–	–	–	Topical	–
Mal de meleda[22]	–	40%	Gel	Topical	–

Malassezia folliculitis[35]	–	–	–	Topical	–
Nail avulsion[52]	–	40%	Liquid	Topical	1 week
Nail debridement[10]	–	20%	Cream	Topical	Once
Nargile (Hubble-Bubble) smoking-induced hand eczema[26]	–	–	Cream	Topical	–
Neurodermatitis[85]	–	10%	Ointment	Topical	30 days
Pachyonychia congenita[6]	–	40%	Paste	Topical	3 months
Papillon-Lefevre syndrome[33]	–	10%	Cream	Topical	–
Pincer nail[17]	–	40%	Paste	Topical	8 months
Pityriasis rubra pilaris[28]	–	20%	–	Topical	–
Postherpetic pruritus[98]	–	10%	Cream	Topical	–
Proliferating trichilemmal cyst[105]	–	–	–	Topical	–
Pruritus[93]	–	20%	Solution	Topical	–
Pseudoscleroderma and eczema craquelé related to nab-paclitaxel treatment[38]	–	20%	Ointment	Topical	–
Psoriasis capitis[123]	–	40%	Ointment	Topical	Up to 3 months
Psoriasiform eruptions related to anti-tumor necrosis factor alpha therapy[32]	–	–	–	Topical	–
Scalp seborrheic dermatitis[123]	–	40%	Ointment	Topical	Up to 3 months
Psoriasis rupioides[47]	–	–	–	Topical	–
Punctate palmoplantar keratoderma[11]	–	10%	Cream	Topical	–

Recessive X-linked ichthyosis[86]	–	10%	Cream	Topical	–
Verrucous hemangiomas[43]	–	10%	Cream	Topical	4 weeks

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Nail avulsion[2,39,64]	1978-1980	• Urea with salicylic acid, distilled water, and Aquaphor	Ointment	20%
		• Urea with anhydrous lanolin, white wax, and white petrolatum base	Ointment	22-40%
		• Urea with white beeswax or paraffin, anhydrous lanolin, white petrolatum, and silica gel type H 10%	Ointment	40%
Cutaneous leishmaniasis[50,88]	1997, 2004	• Urea with paromomycin and white soft paraffin	Ointment	10%
Acne vulgaris[72]	2006	• Urea with benzoyl peroxide	Gel, Cream, or Cleanser	10%
Impetigo[30]	1952	• Urea with sulfathiazole	Powder	25%
Ulcer[87]	1980	• Carbamide peroxide in glycerol	Solution	–
Xerosis of the foot[75]	2011	• Urea with lactic acid, dimethicone, glycerin, stearic and palmitic acids, propylene glycol, povidone, phenoxyehtanol, methyl, ethyl, and propyl parabens, trolamine, and purified water	Foam	35%

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Onychomycosis[49,63,94,99,114]	• Urea with fluconazole, polyvinylpyrrolidone K25, glycerol triacetate, docusate sodium, ethanol, and demineralized water	Solution	20%
	• Urea in Vaseline, lanoline, and white wax	Cream	40%
	• Urea with bifonazole	Ointment	40%
	• Urea with lactic acid, sodium hydroxide, water, and propylene glycol	Solution	10%
	• Urea with butenafine hydrochloride	Cream	20%
Cutaneous leishmaniasis[50,88,101]	• Urea with aminosidine sulphate and white soft paraffin	Ointment	10%
	• Urea with paromomycin and white soft paraffin	Ointment	10%
Psoriasis[70,84]	• Urea with sodium chloride in an oil in water emulsion	Cream	12%
	• Urea niosomal suspension with chitosan dispersed with glacial acetic acid and hydrated for 4-5 hours, glycerin, propylene glycol, and distilled water	Gel	5-10%
Warts[62,89]	• Urea with salicylic acid in petrolatum	Ointment	10%
Atopic dermatitis[76]	• Urea in liquid paraffin, PEG-5 glyceryl stearate, cetyl and stearyl alcohol, stearic acid, tometamol, methyl and propyl parabens, hydrochloric acid, and water	Cream	40%
	• Urea with sodium chloride in liquid paraffin, PEG-5 glyceryl stearate, cetyl and stearyl alcohol, stearic acid, tometamol, methyl and propyl parabens, hydrochloric acid, and water	Cream	40%
Atopic eczema[110]	• Urea in polysorbate 80 (Tween 80), cetomacrogol, anhydrous lanolin, methyl paraben, and distilled water	Cream	10%
	• Urea with commercial betamethasone valerate 0.1% cream	Cream	10%

Ichthyosiform erythroderma[37]	• Urea in Unguentum Merck ®	Cream	15%
Keratitis-ichthyosis-deafness (KID) syndrome[96]	• Urea in Eucerin™	Cream	5, 10%
Plaque psoriasis[66]	• Urea with sodium chloride	Cream	12%
Pruritus[93]	• Urea in lactic acid, Betain, Tween 20, and water	Solution	20%
	• Urea with hydrocortisone in propylene glycol, Tween 20, ethyl alcohol, lactic acid, Betain, sodium chloride, and water	Solution	20%

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 Urea	Interview Summary Response
DER_07	MD	Dermatology Dermatology/Immunology	Independent consultant	Not specified	• Urea is a keratolytic. • Compound for higher concentrations and combination products.

Abbreviation: MD, Doctor of Medicine.

Use of urea

- The interviewee said that urea is a keratolytic and is used for indications like keratosis pilaris and softening nails or thick keratin layers.
    - In lower concentrations, urea is applied to the skin; in high concentrations (40%), it is applied to warts, calluses, or nails.
- The interviewee said that podiatrists will sometimes apply high concentrations of urea to an ugly nail or a plantar wart, wrap it up, and leave it for a week so that the keratin is soft and easy to peel off. This is where one-time in-office applications occur.
    - Comparatively, lower strengths are more for chronic use. Patients may use either the low or higher concentration at home.

Urea in combination with nominated substances

- The interviewee stated that urea with tacrolimus is likely lichen simplex chronicus, prurigo nodularis, psoriasis, or itchy eczema.
- The interviewee said ciclopirox and itraconazole are antifungals; DMSO "is there just to help provide solubility and penetration."
    - The interviewee said that most cases of onychomycosis do not need to be treated; however, people do not like how it looks. Urea softens the nail so that the provider can debride and remove the nail to treat the fungal infection.

Reasons for compounding urea over using the OTC products

- The interviewee provided one reason for the need to obtain higher concentrations of urea; there is no OTC keratolytic that is a high strength (over 20%).
- The interviewee commented that tacrolimus is only available as a solo product. The interviewee said, "people could potentially get tacrolimus ointment point one (0.1) percent and put it on and put urea on top of it, but what you're going to end up with is diluted strength of tacrolimus if you are mixing them together. So if you want one percent tacrolimus with twenty percent urea, the only way you're going to get it is by doing something like this. And I'm not picking on tacrolimus. It's just…it's just an example of one."

Summary of survey results

Table 13. Characteristics of survey respondents [3 people responded to the survey[a]]

Board Certification	MD
Dermatology	3
Pediatric Dermatology	1

[a]Some 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=2[a])
Compounded	1[b]
FDA-approved	2
Over-the-counter	2
Dietary	0
Unsure	0
No response	0

[a]Out of three (3) respondents, two (2) reported using, prescribing, or recommending multiple types of urea product.
[b]One (1) respondent used in combination: "Compounded in white petrolatum or other emollient."

Table 15. Compounded use of urea in practice[a]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Ichthyosis	20-50%	Twice daily	Cream	Topical	2-12 months	All
Callus, corn, hyperkeratosis, keratoderma, psoriasis		–			–	–
Onychomycosis	40-50%					
Tinea capitis	–					

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]One (1) respondent.

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

Indication	Standard Therapy	
	Compounded, n (N=1)	Non-compounded, n (N=1)
Calluses	1	0
Corns	1	0
Hyperkeratosis	1	0
Hypertrophic nails	0	1
Ichthyosis	1	0
Keratodermas	0	1
Onychomycosis	1	0
Psoriasis	0	1
Xerosis	1	0

[a]Some respondents reported more than one (1) indication.

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

Reasons
"The over the counter products containing urea are not effective and any that approach being effective are very hard to find and purchase"

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

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

[a]One (1) respondent wrote "not covered product."

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

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

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

No survey respondents provided this information

CONCLUSION

Urea (UNII code: 8W8T17847W) was nominated for inclusion on the 503B Bulks List and While the wexact medical condition for which the compounded drug is being requested is generally unknown, urea is generally used to promote rehydration of the skin. At higher concentrations, urea is indicated for psoriasis, xerosis, onychomycosis, ichthyosis, eczema, keratosis, keratoderma, corns, and calluses. Urea was nominated for use as a topical product in dosage forms and strengths based on the prescriber's request; the therapeutic dose ranges 10-40%. Out of the foreign medical registries searched, urea is available in Abu Dhabi, Ireland, Namibia, and the UK.

From the literature review, the most common indications in the US were nail avulsion, warts, and hand-foot syndrome in patients taking capecitabine, sorafenib, or sunitinib. The most common indication from the non-US studies was onychomycosis. Compounded urea in topical dosage forms were identified from both US and non-US studies that reflected the nominated indications.

No interviews were conducted.

From the survey responses, two (2) out of three (3) respondents reported using, prescribing, or recommending urea products. One (1) of these respondents reported using compounded urea products for a variety of indications and considered it standard therapy. They reported that OTC urea products are not effective (and if they are, they are difficult to find and purchase). Despite this, the respondent reported using compounded urea less often over the past five years since it is not a covered product.

APPENDICES

Appendix 1. References

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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 **urea**. 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: Urea

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **urea**? 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 urea?... != Compounded drug product Is Not Selected

Skip To: Q2. If What type(s) of product(s) do you use, prescribe, or recommend for urea?... = Compounded drug product Is Selected

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for urea?... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **urea** 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 **urea** 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 urea as a single agent active ingredient, or as on... != Combination Is Not Selected

Display This Question:

If Loop current: Do you use compounded urea as a single agent active ingredient, or as on... = Combination Is Selected

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

- ☐ Urea 10% / Aloe Vera 0.2% / Fluocinolone acetonide 0.05% / Hyaluronic acid sodium salt 0.5% / Lactic acid 10%
- ☐ Urea 10% / Ciclopirox 2% / Ibuprofen 2% / Itraconazole 1% / Terbinafine HCl 4%
- ☐ Urea 20% / Ciclopirox 3% / DMSO 5% / Itraconazole 5%
- ☐ Urea 20% / Hyaluronic acid sodium salt 1% / Tacrolimus 0.1%
- ☐ Urea 20% / Clobetasol propionate 0.05% / Ibuprofen 2% / Mupirocin 5% / Salicylic acid 5%
- ☐ Urea 40% / Aloe Vera 1% / Niacinamide 4%
- ☐ Urea 40% / Aloe Vera 0.5% / Hyaluronic acid sodium salt 0.5% / Salicylic acid 5%
- ☐ Urea 40% / Aloe Vera 1% / Lactic acid 10%
- ☐ Urea 40% / Clobetasol propionate 0.05% / Salicylic acid 4%
- ☐ Other (please describe)_____

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

_____

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

_____

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

_____

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

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded urea in your practice locat... = No

Display This Question:

If Do you stock non-patient-specific compounded urea in your practice locat... = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **urea**? 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 **urea**? 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 **urea**? 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 urea? Please... = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded urea? Please... = Emergencies

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

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

_____

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

_____

End of Block: Urea

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