# Summary Report

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# Amphotericin B

## Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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## Prepared by:

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## REVIEW OF NOMINATIONS

Amphotericin B (UNII code: 7XU7A7DROE) was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc and ASP Cares for the treatment of oral, topical, otic, and vaginal fungal infections. Amphotericin B is nominated for use as multiple dosage forms, including powders, capsules, and oral suspensions, at strengths ranging from 0.02-50%, depending on the indication, form, and route, and routes of administration (ROA), including oral, otic, vaginal, and topical. Additionally, amphotericin B was nominated for use as a 5mg otic capsule to be administered via an insufflator bulb.

One reason provided for nomination to the 503B Bulks List is that the commercially available injectable form is not suited for other ROA due to additional inactive ingredients, mainly deoxycholate. Additionally, the cannot use the commercially available injectable solutions and suspensions cannot be used to compound the otic capsule.

## METHODOLOGY

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of amphotericin B 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, 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 amphotericin B; name variations of amphotericin B 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 amphotericin B. 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 February 26, 2019. The search included a combination of ("amphotericin b"[TIAB] OR "amphotericine b"[TIAB]) AND (capsule OR suspension OR solution OR cream OR ointment OR gel OR oral OR mouth OR otic OR ear OR vagin* OR topical OR skin OR ophthal* OR eye) AND (aspergill*[TIAB] OR candid*[TIAB] OR mycos*[TIAB] OR fungal[TIAB] OR antifungal[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. Amphotericin B is a component of an FDA-approved product, as a result, articles were excluded if amphotericin B was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Additional exclusion criteria included any dosage form/ROA that differed from the nominated dosage form/ROA. Articles were considered relevant based on the identification of a clinical use of amphotericin B or the implementation of amphotericin B 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.

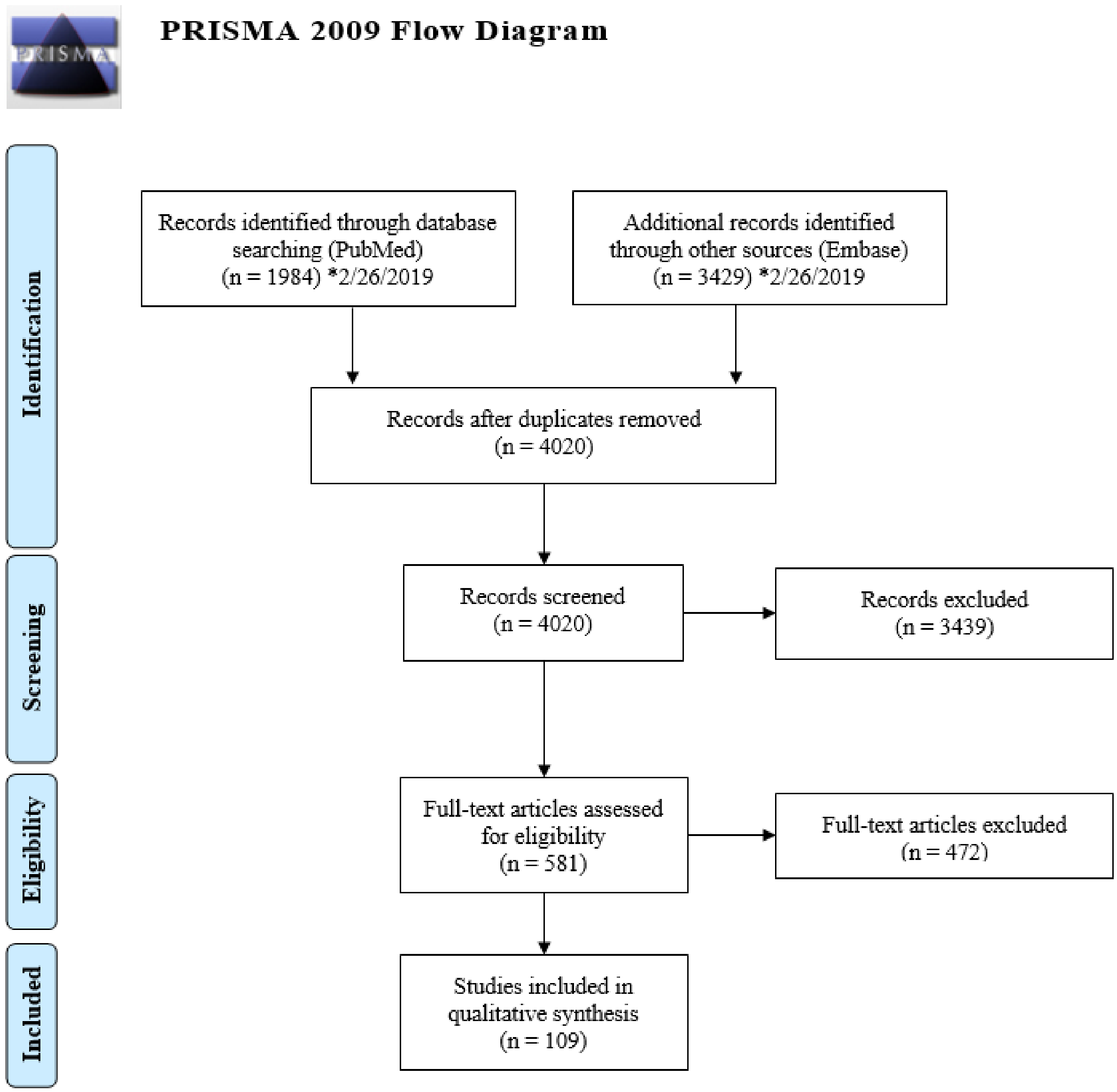
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for amphotericin B 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 amphotericin B 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, five (5) medical specialties that would potentially use amphotericin B were identified: dermatology, infectious disease, obstetrics and gynecology, ophthalmology, and otolaryngology. 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. Four (4) experts were contacted for interviews, of which three (3) accepted and zero (0) declined interviews. One (1) expert specializing in otolaryngology failed to respond to the interview request. 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, infectious disease, obstetrics and gynecology, ophthalmology, and otolaryngology, 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 11 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) |
| Ophthalmology | American Academy of Ophthalmology (AAO) |
| | American Society of Cataract and Refractive Surgery (ASCRS) |
| | American Society of Retina Specialist (ASRS) |

Table 2. Associations that declined participation

| Specialty | Association | Reasons for Declining |
|---|---|---|
| Medicine | American Medical Association (AMA) | Failed to respond |
| | American Osteopathic Association (AOA) | Failed to respond |
| Obstetrics and Gynecology | American College of Obstetricians and Gynecologists (ACOG) | Declined, survey not approved for distribution |
| Otolaryngology | American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) | Failed to respond |
| | American Academy of Otolaryngic Allergy (AAOA) | Declined, stating that they did not think otolaryngologists were the target market for the survey |
| | American Rhinologic Society (ARS) | Declined, stating they do not send out surveys unless they are requested by a member; unable to identify a member to request survey distribution |

## CURRENT AND HISTORIC USE

*Summary of background information*

- Amphotericin B is not available as an FDA-approved product in the nominated dosage forms. However, it is available as an injectable product.
- Amphotericin B is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for amphotericin B.
- Amphotericin B is available in Australia and New Zealand. In Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, New Zealand, Saudi Arabia, and UK, amphotericin B is available as an injectable product.

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]** |
| Amphotericin B | 10mg | Lozenge | Buccal | Australia | Prescription only medicine | 09/30/1991 |
| | | | – | New Zealand | Prescription | 12/31/1969 |

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

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

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

*Summary of literature review*

- Total number of studies included: 109 (70 descriptive, 29 experimental, and 10 observational).
- Most of the studies were from the US (25).
- The most common indication for the use of amphotericin B in the US was fungal keratitis. The most common indications from the non-US studies were antifungal prophylaxis and fungal keratitis.
- Compounded products were identified from both the US and non-US studies. Of these studies, only one (1) did not represent a nominated indication or ROA. The other six (6) were indicated for either oral or vaginal candidiasis, with the corresponding ROA.

Table 5. Types of studies

| Types of Studies | Number of Studies |
|---|---|
| Descriptive[1-70] | 70 |
| Experimental[71-99] | 29 |
| Observational[100-109] | 10 |

Table 6. Number of studies by country

| Country | Number of Studies |
|---|---|
| Australia[7] | 1 |
| Austria[23] | 1 |
| Belgium[73,82] | 2 |
| Brazil[19] | 1 |
| China[36,50,70] | 3 |
| France[9,43,78,81,85,92] | 6 |
| Germany[27,60,79,88,105] | 5 |
| India[21,30,39,52,55,64] | 6 |
| Ireland[37] | 1 |
| Israel[35,100] | 2 |
| Italy[17,42,93,94,101] | 5 |
| Japan[44,46,59,62,63,71,72,75,77,96,98,104,107] | 13 |

| | |
|---|---|
| Korea[31,48,57] | 3 |
| Nepal[8] | 1 |
| The Netherlands[53,54,89,91,95,102,109] | 7 |
| Norway[84] | 1 |
| Saudi Arabia[2] | 1 |
| Spain[18,25,40,41,51] | 5 |
| Switzerland[66] | 1 |
| Taiwan[14] | 1 |
| Thailand[11,12,65] | 3 |
| Tunisia[33,99] | 2 |
| Turkey[4,61] | 2 |
| UK[13,56,68,69,74,76,86] | 7 |
| US[1,3,5,6,10,15,16,20,22,24,26,28,32,34,45,47,49,58,67,87,90,97,103,106,108] | 25 |
| Multiple Countries<br>• Belgium, France, UK, Spain, Germany[83]<br>• Brazil, Chile[29]<br>• Germany, The Netherlands[80]<br>• India, South Africa, Hungary[38] | 4 |
| Total US: 25<br>Total non-US Countries: 84 | |

Table 7. Number of studies by combinations

*No combination products were nominated*

Table 8. Dosage by indication – US

| Indication | Dose | Concentration | Dosage Form | ROA | Duration of Treatment |
|---|---|---|---|---|---|
| Fungal keratitis[5,15,16,20,22,24,28,32,34,47,97,106] | – | – | – | Intracameral | – |
| | – | 0.1-0.15% | Drops, Solution | Ophthalmic | 2 days-6 months |
| Candidiasis[3] (cutaneous[108], cystitis[58], oral[26,45], and vaginitis[6,58,87]) | Daily | 5% | Solution | Intravesical | 5 days |
| | – | – | Solution, Tablets | Oral | – |
| | 25mL/day | 0.02-0.1% | Solution | | |
| | – | 2% | Suspension | | At least 2 months |
| | – | 0.3-4% | Cream, Solution | Vaginal | 7 days |
| | 50mg/day | – | Suppository | | 14 days |
| | – | 2% | Ointment | – | 4-30 days |
| Aspergillus flavus scleritis[10] | – | 0.1% | – | Ophthalmic | – |
| Decontamination of the digestive tract in pediatric liver transplant patients[90] | 400-1000mg | 2% | – | Nasogastric tube | – |
| Fungal crystalline keratopathy[1] | – | – | – | Ophthalmic | 6 weeks |
| Fungal endophthalmitis[49] | – | 0.03% | – | Ophthalmic | – |
| Fungal infection prophylaxis in neutropenic patients[103] | 200mg/day | – | Tablet | Oral | – |
| Papular protothecosis of the chest[67] | – | – | 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 |
|---|---|---|---|---|---|
| Antifungal prophylaxis for asthma patients on inhaled steroids[77], bone marrow transplant[53,72,102,105,109], granulocytopenic cancer[82], hematologic malignancy[17,74,75,79,80,83,89,95,96,98,107], liver transplant[93,94], neutropenia[42,71,73,86,88,101], ventilated pediatric patients[100] | 150-6000mg/day | – | Capsule, Suspension, Syrup, Tablets | Oral | Until neutrophils/granulocytes recover |
| | | | | | Until empiric amphotericin B is started |
| | | | | | Until systemic fungal infection occurs |
| | | | | | As long as ventilated |
| | | | | | 4 days-12 weeks |
| | 40-80mg/day | – | Lozenge | | – |
| | 25mg/kg/day | – | Gargle, Suspension | | 1-112 days |
| | 40-90mL/day | 10% | | | 4 weeks |
| | 20mL/day | 500,000 units/mL | | | – |
| | $300mg/m^2$ | – | Tablet | | – |
| | – | – | Nebulization | – | – |
| Candidiasis (oral[76,78,92,104], cutaneous[44], small intestine[62], vaginal[13,56,68]) | 2400-4800mg/day | – | – | Oral | 4 weeks |
| | 40mg/day | – | Lozenge | | 14 days |
| | 1500mg/day | 10% | Suspension | | 7-14 days |
| | – | 0.2% | Gargle/Solution | – | 1 month-54 days |
| | 100mg/day | – | Gel | Vaginal | 14 days |
| Fungal endophthlamitis[4,27,54] | – | 0.005-0.15% | Drop, Solution | Ophthalmic | – |

| | | | | | |
|---|---|---|---|---|---|
| Fungal keratitis[2,8,9,11,12,14,18,19,21,25,29-31,33,35-41,43,48,50,52,55,57,61,65,66,69,70,99] | – | 0.15% | – | Intracameral | – |
| | – | 0.005-2.5% | Drops, Irrigation solution | Ophthalmic/Topical | At least 2 days-6 months |
| Mucositis[81,85,91] | 1500mg/day | 10% | Suspension | Oral | 7-14 days |
| | | | | | Through the entire hospital stay |
| | 40mg/day | – | Lozenge | – | – |
| Aspergillus fumigatus scleritis[51] | – | 0.3% | – | Topical | – |
| Denture stomatitis[84] | 40mg/day | – | Lozenge | – | 14 days |
| Disseminated *C. albicans* infection[63] | 2800-4000mg/day | – | – | Oral | – |
| Eosinophilic pneumonia (*Aspergillus niger*)[46] | 100-300mg/day | 100mg/mL | Suspension | Oral | – |
| Gut decontamination post-bone marrow transplant[23] | 10mg/kg/day | – | Solution | Oral | – |
| Intraorbital abscess (*Candida allociferrii*)[59] | – | 0.1% | Drops | Topical | – |
| Nasal mycosis[7] | – | – | Drops | Nasal | – |
| Persistent annular erythema[60] | 300mg/day | – | – | Oral | 2 weeks |
| Post-surgical necrotizing subcutaneous infection (*Absidia corymbifera*)[64] | – | – | – | Topical | 4 weeks |

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

Table 10. Compounded products – US

| Indication | Publication Year | Compounding Method | Dosage Form | Final Strength |
|---|---|---|---|---|
| Oral candidiasis[26,45] | 1996, 2002 | • "Compounded suspension" | Suspension | 2% |
| | | • Amphotericin B mixed with sterile water, saliva substitute (glycerin and deionized water), and lemon flavoring | Solution | 0.02-0.1% |
| Candida vaginitis[87] | 2005 | • Amphotericin B was suspended in polyethylene glycol suppository based | Suppository | – |
| Fungal keratitis[20] | 2018 | • "Compounded by a local pharmacy" | Drops | – |

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

| Indication | Compounding Method | Dosage Form | Final Strength |
|---|---|---|---|
| Vaginal candidiasis[13,56,68] | • Obtained from Pharmacy Manufacturing Dept, City General Hospital, Stoke-on-Trent, UK. | Gel | – |
| | • Amphotericin B 100mg with flucytosine 1g in Aquagel | Gel | – |
| | • Amphotericin B 100mg with flucytosine 1g in Aquagel | Gel | – |

Abbreviation: "–", not mentioned.

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

Three (3) interviews were conducted.

Table 12. Overview of interviewees

| Interviewee | Level of Training | Specialty | Current Practice Setting | Experience with Amphotericin B | Interview Summary Response |
|---|---|---|---|---|---|
| DER_07 | MD | Dermatology<br>Dermatology/Immunology | Independent consultant | Yes | • Would not recommend using amphotericin B to treat onychomycosis. |
| INF_01 | MD | Infectious Disease<br>Internal Medicine | Academic medical institution | Yes | • Only uses amphotericin B intravenously. |
| OPH_05 | MD | Ophthalmology | Academic medical institution | Yes | • Uses amphotericin B via injection and topical routes for the eye.<br>• Interested in amphotericin B as office stock, but concerned about sterility with bulk compounding. |

Abbreviation: MD, Doctor of Medicine.

Dosage form

- One (1) interviewee stated that they have never used amphotericin B in any other route besides intravenous.
    - They mentioned being able to see amphotericin B used otically in the future for fungal diseases in the auditory canal or inner ear. However, the interviewee did not specify what type of dosage form would be most appropriate for this route.
    - Did not think amphotericin B had good enough bioavailability to be used in an oral dosage form, except maybe as a topical gastrointestinal (GI) agent to clean the GI tract.
- One (1) interviewee discussed the ophthalmic use of amphotericin B.
    - The interviewee said that they inject it into the eye for endophthalmitis or administer topically for corneal ulcers. However, they stated that it is rarely used as an eye drop and that "All these weird corneal ulcers rarely happen."

- One (1) interviewee discussed topical amphotericin B for treating onochomycosis or paronychia. However, they said that there are other anti-fungal agents for these conditions; they do not know why one would use amphotericin B. Onychomycosis is mostly caused by the trichophyton species, but amphotericin B does not have great activity against it; “It’s really much more to me a yeast drug.”
    - The interviewee said that overall, they advise against treating onochomycotic nails because they are likely to re-infect the nail. Treatment would have to continue until the nail has completely regrown, which can take a year for toenails; “the problem is that the dead kerytotic nail will still have active fungi that’s still present in the nail plate for as long as it takes to grow out.”
        - The interviewee themselves would probably not use it but said that someone who is desperate might.
    - The interviewee also stated that in situations where someone has a deep fungal infection with a cutaneous manifestation, you cannot treat them topically. They must be given systemic agents because it has disseminated from a systemic source.

Office stock

- One (1) interviewee stated that if the patient had a fungal infection bad enough to require amphotericin B, they would be admitted to the hospital. Therefore, would not anticipate needing to keep office stock in an outpatient setting. In addition, most of the fungal infections they see in the outpatient setting are pulmonary infections, and typically those patients do well with itraconazole.
- One (1) interviewee stated that would be interested in amphotericin B as office stock, because if needed, it is an emergency and must be administered within a couple of hours.
    - The interview stated that one issue with administering commercially available amphotericin B into the eye is that it is not the right concentration. When injecting amphotericin B, the interviewee has the pharmacy mix it to the concentration needed. “Certain antibiotics, like if you put the wrong dose in, you'll toast the retina, and the eye is done.”
    - The interviewee commented that when they were a fellow, they had to mix their antibiotics at their desk, and there were concerns about sterility and accuracy. “I would 100% rather order it from a pharmacy and have it done appropriately. First of all, it takes a lot of time, and second of all, we don't feel comfortable with that. I want it done right.” However, if the practitioner is outpatient, there is no inpatient pharmacy.
    - While the interviewee is interested in having amphotericin B more available in the office, they would prefer the outsourcing facility to start from the already sterile commercially available product compared to bulk and having to sterilize it.
    - When asked about the stinging with injecting commercial amphotericin B into the eye, the interviewee was not concerned, “if you have a corneal ulcer that you're going to lose your eye over, you're not going to care that it stings upon administration. It's so infrequently used. That seems silly to me. But I think, either way you could get the drug in your office so that it would be more convenient to the patient, then I guess I would do it with the most sterile way, which is the originally approved.”

Supplemental information

- One (1) interviewee provided a review article regarding the use of amphotericin B in refractory cases of onychomycosis.[110]

- Daily topical application of intravenous amphotericin B solution in a mixture of DMSO and isopropyl alcohol (final concentration 2mg/mL) was listed for onychomycosis caused by molds (such as *Fusarium* sp., *Acremonium* sp., and *Aspergillus* sp.) that were non-responsive to classical antifungal therapies.[111] All eight (8) of the patients treated were determined to be clinically cured after being treated with the topical amphotericin B for 12 months; one (1) patient received therapy for 11 months and another had a treatment duration of 23 months.[111]

*Summary of survey results*

Table 13. Characteristics of survey respondents [76 people responded to the survey[a]]

| Board Certification | MD | ND | No Response |
|---|---|---|---|
| Cardiovascular Disease | 0 | 1 | 0 |
| Dermatology | 2 | 0 | 0 |
| Internal Medicine | 2 | 0 | 0 |
| Ophthalmology | 40 | 0 | 0 |
| No Response | 0 | 0 | 33 |

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner.
[a]Some respondents reported more than one (1) board certification.

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

| Types of Products | Respondents, n (N=45[a]) |
|---|---|
| Compounded | 37[b] |
| FDA-approved | 8 |
| Over-the-counter | 1 |
| Dietary | 1 |
| Unsure | 3 |
| No Response | 2 |

[a]Out of 76 respondents, 45 reported using, prescribing, or recommending multiple types of amphotericin B product.
[b]Five (5) respondents used in combination with natamycin and/or voriconazole.

Table 15. Compounded use of amphotericin B in practice[a,b]

| Indication | Strength | Dosing frequency | Dosage Form | ROA | Duration of Treatment | Patient Population |
|---|---|---|---|---|---|---|
| Endophthalmitis (*Candida*, fungal, infectious) | 5mcg/0.1mL | Every 3 days | Solution | Intravitreal injection | 2 weeks | Often iatrogenic, chronic debilitated patients |
| | 5mcg | "1" | | | Once | |
| | 1.5mg/mL | Hourly | Drop | Topical | As indicated by patient condition | Any |
| Keratitis (*Candida*, fungal) | 0.1mg | As needed | Solution or suspension? | Intracorneal injection | As needed | Any<br>Those who don't respond to other drugs<br>Typically elderly patients<br>Random<br>10% |
| | 0.15% | Every 1-2 hours | Drop, Solution | Eye, Topical | 7 days-3 months<br>As indicated by patient condition | |
| | 0.2% | Hourly to 4x/day | Eye drops | | 1-6 weeks | |
| Fungal canaliculitis | 0.15% | Four times per day | – | Topical | 1 month | Random |
| Fungal corneal ulcer | 0.05-0.5% | Every 1-2 hours | Drops, Ocular Drops | Drops, Topical, Ophthalmic | Weeks<br>As long as needed | Adults and children<br>Cornea ulcers |
| | "0.001" | Hourly to 4x/day | Topical, injection | Topical, injection | Days to weeks to months | Fungal infection |
| Fungal scleritis | 0.05% | Hourly | Ocular drops | Topical drops | As long as needed | Adults and children |
| Recalcitrant fungal keratitis | 0.01% | "Once in OR" | – | Intracameral | One time | – |

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Twenty-one (21) respondents.
[b]Quotations are direct from respondents.

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

| Indication | Standard Therapy | | | |
|---|---|---|---|---|
| | **Compounded, n (N=37)** | **Non-compounded, n (N=3)** | **Unsure, n (N=3)** | **No Response, n (N=2)** |
| Canaliculitis | 1 | 0 | 0 | 0 |
| Endophthalmitis (*Candida*, fungal) | 6 | 0 | 1 | 0 |
| Keratitis (candida, fungal[b]) | 11 | 3 | 2 | 0 |
| Fungal corneal ulcer | 2 | 0 | 0 | 0 |
| Yeast keratitis | 2 | 0 | 0 | 0 |
| No Response | 18 | 0 | 0 | 2 |

Abbreviation: "–", not mentioned.
[a]Some respondents reported more than one indication.
[b]One (1) respondent specified: "Any fungal keratitis that is susceptible to amphotericin."

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

| Theme | Reasons |
|---|---|
| Availability | Ophthalmic availability<br>• “No FDA approved ophthalmic drop exists”<br>• “No FDA approved injections for intraocular use” |
| | FDA-approved alternatives<br>• “Lack of available FDA-approved alternatives”<br>• “No approved alternative”<br>• “No commercially available alternative”<br>• “No other option” |
| | FDA-approved product<br>• “FDA product not available”<br>• “There isn’t any FDA-approved drug for this route of administration”<br>• “There is no FDA approved product”<br>• “Not available”<br>• “None available” |
| Cost | “Cost” |
| Efficacy | Compared to natamycin<br>• “Best agent for killing candida yeast; only 1 FDA product is available for fungal corneal ulcers (Natacyn) and we can’t always get it”<br>• “Infection refractory to Natamycin”<br>• “Natamycin 5% may prove ineffective in advanced fungal keratitis” |
| | Standard of care<br>• “It is more effective against candida than other available meds. It is the drug of choice for candida ocular infections”<br>• “It is the standard of care for fungal keratitis especially in candida infections. All FDA approved products are ineffective or less effective”<br>• “No comparable product” |
| Provider preference | “Nor is it the FDAs role to tell me how to take care of patients” |

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

| | **Respondents, n (N=37)** |
|---|---|
| No–use has remained consistent | 15 |
| Yes–I use it LESS often now<br>• "Can't find it"<br>• "Alternative drops"<br>• "Oral drugs often work" | 3 |
| Yes–I use it MORE often now<br>• "Increase in fungal ulcers"<br>• "Seeing more fungal corneal ulcers"<br>• "Patient population"<br>• "Works better" | 5 |
| No Response | 14 |

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

| | **Respondents, n (N=37)** |
|---|---|
| No | 20 |
| Yes | 3 |
| No Response | 14 |

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

| | **Respondents, n (N=3)** |
|---|---|
| **In what practice locations do you stock non-patient-specific compounded amphotericin B?** | |
| Physician office | 2 |
| Outpatient clinic | 0 |
| Emergency room | 0 |
| Operating room | 0 |
| Inpatient ward | 0 |
| No Response | 1 |
| **How do you obtain your stock of non-patient-specific compounded amphotericin B?** | |
| Purchase from a compounding pharmacy | 1 |
| Purchase from an outsourcing facility | 1 |
| Compound the product yourself | 0 |
| No Response | 1 |
| **Why do you keep a stock of non-patient-specific compounded amphotericin B?** | |
| Convenience | 0 |
| Emergencies | 2 |
| No Response | 1 |

## CONCLUSION

Amphotericin B (UNII code: 7XU7A7DROE) was nominated for inclusion on the 503B Bulks List for the treatment of oral, topical, otic, and vaginal fungal infections via a variety of dosage forms and ROA, depending on the location of the infection being treated. Amphotericin B is available as an FDA-approved product, but not in the nominated dosage forms; only as an injectable product. Out of the other national medical registries searched, non-injectable amphotericin B is only available in Australia and New Zealand, where it is available as a lozenge.

From the literature review conducted, six (6) of the seven (7) studies that reported compounding amphotericin B were indicated for either oral or vaginal candidiasis, both of which were indications provided from the nominations. However, the most common indication for amphotericin B in the US was fungal keratitis, and the most common indications for non-US studies were antifungal prophylaxis and fungal keratitis.

From the interviews, one (1) interviewee reported only using amphotericin B intravenously and the only other route that they could potentially see is optical; however the dosage form was not specificed.  One (1) interviewee does use ophthalmic amphotericin B.  They expressed interest in having it available as office stock but expressed concern about maintaining sterility with compounding from bulk powders over commercially available products.  The interviewee was not troubled about the possibility of stinging with commercially available amphotericin B since it is infrequently used in this manner, and when it is the patient is at risk for losing the eye, so stinging is not a concern.

From the survey, 45 out of 76 respondents reported using, prescribing, or recommending multiple types of amphotericin B products, 37 of which reported using compounded amphotericin B.  Five (5) respondents reported using amphotericin B in combination with natamycin and/or voriconazole.  All the submitted indications for compounded amphotericin B were for ophthalmic disorders.  The most common indication respondents used compounded amphotericin B for was keratitis, followed by endophthalmitis. The main reasons for using compounded amphotericin B products over an FDA-approved product were availability (since no FDA approved ophthalmic drop or injection exists), cost, and effectiveness compared to other approved medications.  Of the 37 respondents who reported using compounded amphotericin B, 15 stated no change in use of the compounded product over the past 5 years.  Three (3) stated they use it less often now, and five (5) stated they use it more often.  Three (3) respondents reported stocking non-patient-specific compounded amphotericin B in their practice; two (2) in the physician office, both for emergencies.  One (1) of these respondents reported purchasing from a compounding pharmacy; the other reported purchasing from an outsourcing facility.

# APPENDICES

## *Appendix 1. References*


1. Ainbinder DJ, Parmley VC, Mader TH, Nelson ML. Infectious crystalline keratopathy caused by Candida guilliermondii. *American Journal of Ophthalmology.* 1998;125(5):723-725.
2. Al-Assiri A, Al-Jastaneiah S, Al-Khalaf A, Al-Fraikh H, Wagoner MD. Late-onset donor-to-host transmission of Candida glabrata following corneal transplantation. *Cornea.* 2006;25(1):123-125.
3. Alban J. ORAL AMPHOTERICIN B IN THE MANAGEMENT OF CUTANEOUS AND MUCOSAL CANDIDIASIS. *Dermatologia tropica et ecologica geographica.*18:217-220.
4. Aydin S, Ertugrul B, Gultekin B, Uyar G, Kir E. Treatment of two postoperative endophthalmitis cases due to Aspergillus flavus and Scopulariopsis spp. with local and systemic antifungal therapy. *BMC Infectious Diseases.* 2007;7((Kir E., erkinkir@yahoo.com) Adnan Menderes University Medical Faculty, Department of Ophthalmology, Aydin, Turkey).
5. Banitt M, Berenbom A, Shah M, Buxton D, Milman T. A case of polymicrobial keratitis violating an intact lens capsule. *Cornea.* 2008;27(9):1057-1061.
6. Baum SE, Morris JT. Amphotericin B douche for highly resistant Candida (Torulopsis) glabrata vaginitis. *Infections in Medicine.* 2001;18(2):114-117.
7. Baumgart K, Motum P, Benson W. Recurrent epistaxis chronic pancytopenia and nasal mycosis. *Pathology.* 1990;22(2):111-114.
8. Borroni D, Pandey A, Lace I, Drucka E, Zemitis A. Corneal fungal infections: evaluation and treatment. *Investigative Ophthalmology and Visual Science.* 2017;58(8).
9. Bourcier T, Touzeau O, Thomas F, et al. Candida Parapsilosis keratitis. *Cornea.* 2003;22(1):51-55.
10. Carlson AN, Foulks GN, Perfect JR, Kim JH. Fungal scleritis after cataract surgery: Successful outcome using itraconazole. *Cornea.* 1992;11(2):151-154.
11. Chaidaroon W, Tananuvat N, Chavengsaksongkram P, Vanittanakom N. Corneal chromoblastomycosis caused by Fonsecaea pedrosoi. *Case Reports in Ophthalmology.* 2015;6(1):82-87.
12. Chaidaroon W, Tantayakom T. Nocardia keratitis in a human immunodeficiency virus patient. *Japanese Journal of Ophthalmology.* 2004;48(3):272-275.
13. Challenor R, Pinsent S, Ekanayaka R. A case series of the management of symptomatic azole-resistant candida. *International Journal of STD and AIDS.* 2012;23(5):375-376.
14. Chen WL, Tsai YY, Lin JM, Chiang CC. Unilateral candida parapsilosis interface keratitis after laser in Situ keratomileusis-case report and review of the literature. *Cornea.* 2009;28(1):105-107.
15. Choi DM, Goldstein MH, Salierno A, Driebe WT. Fungal keratitis in a daily disposable soft contact lens wearer. *CLAO Journal.* 2001;27(2):111-112.
16. Currie D. MYCOTIC KERATITIS. THREE CASES WITH A COMMON ETIOLOGIC FACTOR. *Archives of ophthalmology (Chicago, Ill : 1960).* 1963;70:335-336.
17. D'Antonio D, Iacone A, Schioppa FS, Bonfini T, Romano F. Effect of the current antimicrobial therapeutic strategy on fungal colonization in patients with hematologic malignancies. *Current Microbiology.* 1996;33(2):118-122.

18. Díaz-Valle D, Del Castillo JMB, Amor E, Toledano N, Carretero MM, Díaz-Valle T. Severe keratomycosis secondary to Scedosporium apiospermum. *Cornea.* 2002;21(5):516-518.

19. Do Nascimento HM, De Oliveira LA, Höfling-Lima AL. Infectious keratitis in patients undergoing Boston Type 1 keratoprosthesis (Boston KPro) procedure: Case series. *Arquivos Brasileiros de Oftalmologia.* 2011;74(2):127-129.

20. Doshi H, Pabon S, Price MO, Feng MT, Price FW. Overview of systemic Candida infections in hospital settings and report of Candida after DMEK successfully treated with antifungals and partial graft excision. *Cornea.* 2018;37(8):1071-1074.

21. Dudeja L, Jeganathan L, Prajna NV, Prajna L. Fungal keratitis caused by Laetisaria arvalis. *Indian journal of medical microbiology*.36(1):140-142.

22. Edelstein SL, Akduman L, Durham BH, Fothergill AW, Hsu HY. Resistant fusarium keratitis progressing to endophthalmitis. *Eye and Contact Lens.* 2012;38(5):331-335.

23. Emminger W, Lang HRM, Emminger-Schmidmeier W, Peters C, Gadner H. Amphotericin B serum levels in pediatric bone marrow transplant recipients. *Bone Marrow Transplantation.* 1991;7(2):95-99.

24. Farjo QA, Farjo RS, Farjo AA. Scytalidium keratitis: Case report in a human eye. *Cornea.* 2006;25(10):1231-1233.

25. Ferrer C, Montero J, Alió JL, Abad JL, Ruiz-Moreno JM, Colom F. Rapid molecular diagnosis of posttraumatic keratitis and endophthalmitis caused by Alternaria infectoria. *Journal of Clinical Microbiology.* 2003;41(7):3358-3360.

26. Grim SA, Smith KM, Romanelli F, Ofotokun I, Pérez A, Kaiser JM. Treatment of azole-resistant oropharyngeal candidiasis with topical amphotericin B. *Annals of Pharmacotherapy.* 2002;36(9):1383-1386.

27. Grueb M, Rohrbach JM, Zierhut M. Amphotericin B in the therapy of Candida glabrata endophthalmitis after penetrating keratoplasty. *Cornea.* 2006;25(10):1243-1244.

28. Heidemann DG, Dunn SP, Watts JC. Aspergillus keratitis after radial keratotomy. *American Journal of Ophthalmology.* 1995;120(2):254-256.

29. Höfling-Lima AL, Guarro J, De Freitas D, et al. Clinical treatment of corneal infection due to Fonsecaea pedrosoi - Case report. *Arquivos Brasileiros de Oftalmologia.* 2005;68(2):270-272.

30. Jhanji V, Sharma N, Mannan R, Titiyal JS, Vajpayee RB. Management of tunnel fungal infection with voriconazole. *Journal of Cataract and Refractive Surgery.* 2007;33(5):915-917.

31. Jung SW, Kwon YA, Lee MK, Song SW. Epidermophyton fungal keratitis following laser-assisted subepithelial keratectomy. *Journal of cataract and refractive surgery.* 2009;35(12):2157-2160.

32. Keating A, Pineda R. Trichosporon asahii keratitis in a patient with a type I Boston keratoprosthesis and contact lens. *Eye & contact lens.* 2012;38(2):130-132.

33. Khochtali S, Hriz A, Abid F, Khairallah-Ksiaa I, Jelliti B, Khairallah M. Alternaria keratitis after uneventful phacoemulsification in an otherwise healthy adult. *Journal of Ophthalmic Inflammation and Infection.* 2016;6(1):1-3.

34. Knape RM, Motamarry SP, Sakhalkar MV, Tuli SS, Driebe WT. Pseudodendritic fungal epithelial keratitis in an extended wear contact lens user. *Eye and Contact Lens.* 2011;37(1):36-38.

35. Kremer I, Goldenfeld M, Shmueli D. Fungal keratitis associated with contact lens wear after penetrating keratoplasty. *Annals of ophthalmology.* 1991;23(9):342-345.

36. Li STL, Yiu EPF, Wong AHY, Yeung JCT, Yu LWH. Successful Treatment of Lasiodiplodia theobromae Keratitis - Assessing the Role of Voriconazole. *Case Reports in Ophthalmology.* 2016;7(3):179-185.

37. Lotery AJ, Kerr JR, Page BA. Fungal keratitis caused by Scopulariopsis brevicaulis: successful treatment with topical amphotericin B and chloramphenicol without the need for surgical debridement. *The British journal of ophthalmology.* 1994;78(9):730.

38. Manikandan P, Vismer HF, Kredics L, et al. Corneal ulcer due to Neocosmospora vasinfecta in an immunocompetent patient. *Medical mycology.* 2008;46(3):279-284.

39. Mehta H, Mehta HB, Garg P, Kodial H. Voriconazole for the treatment of refractory Aspergillus fumigatus keratitis. *Indian Journal of Ophthalmology.* 2008;56(3):243-245.

40. Mendicute J, Ondarra A, Eder F, Ostolaza JI, Salaberria M, Lamsfus JM. The use of collagen shields impregnated with amphotericin B to treat Aspergillus keratomycosis. *CLAO Journal.* 1995;21(4):252-255.

41. Mendicute J, Orbegozo J, Ruiz M, Sáiz A, Eder F, Aramberri J. Keratomycosis after cataract surgery. *Journal of Cataract and Refractive Surgery.* 2000;26(11):1660-1666.

42. Menichetti F, Del Favero A, Martino P, et al. Preventing fungal infection in neutropenic patients with acute leukemia: Fluconazole compared with oral amphotericin B. *Annals of Internal Medicine.* 1994;120(11):913-918.

43. Merle H, Guyomarch J, Joyaux JC, Dueymes M, Donnio A, Desbois N. Keratomycosis complicating pterygium excision. *Clinical Ophthalmology.* 2011;5(1):1435-1437.

44. Mochizuki T, Urabe Y, Hirota Y, Watanabe S, Shiino A. A case of Candidia albicans skin abscess associated with intravenous catheterization. *Dermatologica.* 1988;177(2):115-119.

45. Nguyen MT, Weiss PJ, LaBarre RC, Miller LK, Oldfield EC, Wallace MR. Orally administered amphotericin B in the treatment of oral candidiasis in HIV-infected patients caused by azole-resistant Candida albicans. *AIDS (London, England).* 1996;10(14):1745-1747.

46. Ogawa H, Fujimura M, Tofuku Y, Kitagawa M. Eosinophilic pneumonia caused by Aspergillus niger: Is oral cleansing with amphotericin B efficacious in preventing relapse of allergic pneumonitis? *Journal of Asthma.* 2009;46(1):95-98.

47. Oostra TD, Schoenfield LR, Mauger TF. Candida dubliniensis: A novel cause of fungal keratitis. *IDCases.* 2018;14((Schoenfield L.R.) Department of Pathology, The Ohio State University Wexner Medical Center, 410 W 10th Avenue, Columbus, Ohio, United States).

48. Park KA, Ahn K, Chung ES, Chung TY. Pichia anomala fungal keratitis. *Cornea.* 2008;27(5):619-620.

49. Patel AS, Hemady RK, Rodrigues M, Rajagopalan S, Elman MJ. Endogenous Fusarium endophthalmitis in a patient with acute lymphocytic leukemia. *American Journal of Ophthalmology.* 1994;117(3):363-368.

50. Qiu WY, Yao YF. Mycotic keratitis caused by concurrent infections of Exserohilum mcginnisii and Candida parapsilosis. *BMC ophthalmology.* 2013;13(1):37.

51. Rodriguez-Ares MT, De Rojas Silva MV, Pereiro M, Fente Sampayo B, Gallegos Chamas G, M SS. Aspergillus fumigatus scleritis. *Acta Ophthalmologica Scandinavica.* 1995;73(5):467-469.

52. Sangwan J, Lathwal S, Juyal D, Sharma N. Fonsecaea pedrosoi: A rare etiology in fungal keratitis. *Journal of Clinical and Diagnostic Research.* 2013;7(10):2272-2273.

53. Schattenberg A, De Vries F, De Witte T, Cohen O, Donnelly J, De Pauw BE. Allogeneic bone marrow transplantation after partial lobectomy for aspergillosis of the lung. *Bone Marrow Transplantation.* 1988;3(5):509-512.

54. Schotveld JH, Raijmakers AJW, Henry Y, Zaal MJW. Donor-to-host transmitted Candida endophthalmitis after penetrating keratoplasty. *Cornea.* 2005;24(7):887-889.

55. Sengupta J, Saha S, Khetan A, Ganguly A, Banerjee D. Candida fermentati: A rare yeast involved in fungal keratitis. *Eye and Contact Lens.* 2013;39(4):e15-e18.

56. Shann S, Wilson J. Treatment of Candida glabrata using topical amphotericin B and flucytosine. *Sexually transmitted infections.* 2003;79(3):265-266.

57. Shin JY, Kim HM, Hong JW. Keratitis caused by Verticillium species. *Cornea.* 2002;21(2):240-242.

58. Sivasubramanian G, Sobel JD. Refractory urinary tract and vulvovaginal infection caused by Candida krusei. *International urogynecology journal and pelvic floor dysfunction.* 2009;20(11):1379-1381.

59. Soki H, Abo K, Yamazaki K, et al. First report of intraorbital abscess caused by Candida allociferrii and specific PCR for differentiating stephanoascus ciferrii complex species. *Japanese Journal of Medical Mycology.* 2015;56(2):E9-E14.

60. Stachowitz S, Abeck D, Schmidt T, Ring J. Persistent annular erythema of infancy associated with intestinal Candida colonization. *Clinical and Experimental Dermatology.* 2000;25(5):404-405.

61. Tamcelik N, Ozdamar A, Kizilkaya M, Devranoglu K, Ustundag C, Demirkesen C. Fungal keratitis after nonpenetrating glaucoma surgery. *Cornea.* 2002;21(5):532-534.

62. Tamura H, Yamashita S, Kusano N, et al. Fulminant hepatitis complicated by small intestine infection and massive hemorrhage. *Journal of Gastroenterology.* 1998;33(3):412-418.

63. Tanaka J, Kasai M, Masauzi N, et al. Successful second allogeneic bone marrow transplantation in a relapsed acute myeloid leukemia patient with fungal liver abscess. *Annals of Hematology.* 1992;65(4):193-195.

64. Thami GP, Kaur S, Bawa AS, Chander J, Mohan H, Bedi MS. Post-surgical zygomycotic necrotizing subcutaneous infection caused by Absidia corymbifera. *Clinical and Experimental Dermatology.* 2003;28(3):251-253.

65. Thanathanee O, Bhoomibunchoo C, Anutarapongpan O, Suwan-Apichon O, Yospaiboon Y. Successful treatment of chrysosporium keratitis with voriconazole. *International Medical Case Reports Journal.* 2017;10((Thanathanee O.; Bhoomibunchoo C.; Anutarapongpan O.; Suwan-Apichon O.; Yospaiboon Y., yosanan@kku.ac.th) KKU Eye Center, Department of Ophthalmology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand):93-95.

66. Theoulakis P, Goldblum D, Zimmerli S, Muehlethaler K, Frueh BE. Keratitis resulting from Thielavia subthermophila Mouchacca. *Cornea.* 2009;28(9):1067-1069.

67. Tyring SK, Lee PC, Walsh P, Garner JF, Little WP. Papular protothecosis of the chest. Immunologic evaluation and treatment with a combination of oral tetracycline and topical amphotericin B. *Archives of Dermatology.* 1989;125(9):1249-1252.

68. White DJ, Habib AR, Vanthuyne A, Langford S, Symonds M. Combined topical flucytosine and amphotericin B for refractory vaginal Candida glabrata infections. *Sexually Transmitted Infections.* 2001;77(3):212-213.

69. Wilde C, Messina M, Moshiri T, Snape SE, Maharajan S. Interface Scopulariopsis gracilis fungal keratitis following Descemet's stripping automated endothelial keratoplasty (DSAEK) with a contaminated graft. *International ophthalmology.* 2018;38(5):2211-2217.

70. Wu PC, Lai CH, Tan HY, Ma DH, Hsiao CH. The successful medical treatment of a case of paecilomyces lilacinus keratitis. *Cornea.* 2010;29(3):357-358.

71. Akiyama H, Mori S, Tanikawa S, Sakamaki H, Onozawa Y. Fluconazole versus oral amphotericin B in preventing fungal infection in chemotherapy-induced neutropenic patients with haematological malignancies. *Mycoses.* 1993;36(11-12):373-378.

72. Ashida T, Tsubaki K, Hasegawa H, Kanamaru A. A comparative study of changes in fecal flora in patients preconditioned with either amphotericin B or fluconazole for allogeneic bone marrow transplantation. *Kansenshogaku zasshi The Journal of the Japanese Association for Infectious Diseases.* 2000;74(4):365-371.

73. Boogaerts M, Maertens J, van Hoof A, et al. Itraconazole versus amphotericin B plus nystatin in the prophylaxis of fungal infections in neutropenic cancer patients. *The Journal of antimicrobial chemotherapy.* 2001;48(1):97-103.

74. Donnelly JP, Starke ID, Galton DA, Catovsky D, Goldman JM, Darrell JH. Oral ketoconazole and amphotericin B for the prevention of yeast colonization in patients with acute leukaemia. *The Journal of hospital infection.* 1984;5(1):83-91.

75. Ezaki K, Hirano M, Ohno R, et al. Evaluation of the prophylactic effect of oral amphotericin B on fungal infection. Comparative studies using two dosage regimens. *Acta Haematologica Japonica.* 1990;53(7):1147-1155.

76. Finlay PM, Richardson MD, Robertson AG. A comparative study of the efficacy of fluconazole and amphotericin B in the treatment of oropharyngeal candidosis in patients undergoing radiotherapy for head and neck tumours. *British Journal of Oral and Maxillofacial Surgery.* 1996;34(1):23-25.

77. Fukushima C, Shimoda T, Kawano T, et al. Effects of amphotericin B gargles on oral colonization of Candida albicans in asthmatic patients on steroid inhalation therapy. *Respiration.* 2001;68(5):465-470.

78. Gligorov J, Bastit L, Gervais H, et al. Prevalence and treatment management of oropharyngeal candidiasis in cancer patients: Results of the French candidoscope study. *International Journal of Radiation Oncology Biology Physics.* 2011;80(2):532-539.

79. Kern W, Behre G, Rudolf T, et al. Failure of fluconazole prophylaxis to reduce mortality or the requirement of systemic amphotericin B therapy during treatment for refractory acute myeloid leukemia: results of a prospective randomized phase III study. German AML Cooperative Group. *Cancer.* 1998;83(2):291-301.

80. Kurrle E, Dekker AW, Gaus W. Prevention of infection in acute leukemia: A prospective randomized study on the efficacy of two different drug regimens for antimicrobial prophylaxis. *Infection.* 1986;14(5):226-232.

81. Lefebvre JL, Domenge C. A comparative study of the efficacy and safety of fluconazole oral suspension and amphotericin B oral suspension in cancer patients with mucositis. *Oral Oncology.* 2002;38(4):337-342.

82. Meunier F, Aoun M, Janssens M, Dekoster C, Paesmans M. Chemoprophylaxis of fungal infections in granulocytopenic patients using fluconazole vs oral amphotericin B. *Drug Investigation.* 1991;3(4):258-265.

83. Ninane J, Gluckman E, Gibson BS, et al. A multicentre study of fluconazole versus oral polyenes in the prevention of fungal infection in children with hematological or oncological malignancies. *European Journal of Clinical Microbiology and Infectious Diseases.* 1994;13(4):330-337.

84. Olsen I. Denture stomatitis. The clinical effects of chlorhexidine and amphotericin B. *Acta odontologica Scandinavica.* 1975;33(1):47-52.

85. Orvain C, Moles-Moreau MP, François S, et al. Miconazole mucoadhesive buccal tablet in high-dose therapy with autologous stem cell transplantation (HDT/ASCT)-induced mucositis. *Supportive Care in Cancer.* 2014;23(2):359-364.

86. Paterson PJ, McWhinney PHM, Potter M, Kibbler CC, Prentice HG. The combination of oral amphotericin B with azoles prevents the emergence of resistant Candida species in neutropenic patients. *British Journal of Haematology.* 2001;112(1):175-180.

87. Phillips AJ, Stucky V, Golditch I, et al. Treatment of non-albicans Candida vaginitis with amphotericin B vaginal suppositories. *American Journal of Obstetrics and Gynecology.* 2005;192(6):2009-2013.

88. Philpott-Howard JN, Wade JJ, Mufti GJ, Brammer KW, Ehninger G. Randomized comparison of oral fluconazole versus oral polyenes for the prevention of fungal infection in patients at risk of neutropenia. Multicentre Study Group. *The Journal of antimicrobial chemotherapy.* 1993;31(6):973-984.

89. Rozenberg-Arska M, Dekker AW, Branger J, Verhoef J. A randomized study to compare oral fluconazole to amphotericin B in the prevention of fungal infections in patients with acute leukaemia. *The Journal of antimicrobial chemotherapy.* 1991;27(3):369-376.

90. Smith SD, Jackson RJ, Hannakan CJ, Wadowsky RM, Tzakis AG, Rowe MI. Selective decontamination in pediatric liver transplants. A randomized prospective study. *Transplantation.* 1993;55(6):1306-1309.

91. Stokman MA, Spijkervet FKL, Burlage FR, et al. Oral mucositis and selective elimination of oral flora in head and neck cancer patients receiving radiotherapy: A double-blind randomised clinical trial. *British Journal of Cancer.* 2003;88(7):1012-1016.

92. Taillandier J, Esnault Y, Alemanni M. A comparison of fluconazole oral suspension and amphotericin B oral suspension in older patients with oropharyngeal candidosis. *Age and Ageing.* 2000;29(2):117-123.

93. Tortorano AM, Viviani MA, Pagano A, et al. Candida colonization in orthotopic liver transplantation: Fluconazole versus oral amphotericin B. *Journal de Mycologie Medicale.* 1995;5(1):21-24.

94. Viviani MA, Tortorano AM, Malaspina C, et al. Surveillance and treatment of liver transplant recipients for candidiasis and aspergillosis. *European Journal of Epidemiology.* 1992;8(3):433-436.

95. Vreugdenhil G, Van Dijke BJ, Donnelly JP, et al. Efficacy of itraconazole in the prevention of fungal infections among neutropenic patients with hematologic malignancies and intensive chemotherapy: A double blind, placebo controlled study. *Leukemia and Lymphoma.* 1993;11(5-6):353-358.

96. Watanabe N, Matsumoto K, Kojima S, Kato K. Invasive fungal infections in pediatric patients with hematologic malignancies receiving oral amphotericin b solution and early intravenous administration of fluconazole. *Journal of Pediatric Hematology/Oncology.* 2011;33(4):270-275.

97. Wood TO, Williford W. Treatmen of keratomycosis with amphotericin B 0.15%. *American journal of ophthalmology.* 1976;81(6):847-849.

98. Yamada T, Dan K, Nomura T. Prevention of bacterial and fungal infections in acute leukemia patients: A new and potent combination of oral norfloxacin and amphotericin B. *Internal Medicine.* 1993;32(9):710-715.

99. Zbiba W, Baba A, Bouayed E, Abdessalem N, Daldoul A. A 5-year retrospective review of fungal keratitis in the region of Cap Bon. *Journal francais d'ophtalmologie.* 2016;39(10):843-848.

100. Ben-Ari J, Samra Z, Nahum E, Levy I, Ashkenazi S, Schonfeld TM. Oral amphotericin B for the prevention of Candida bloodstream infection in critically ill children. *Pediatric Critical Care Medicine.* 2006;7(2):115-118.

101. De Laurenzi A, Matteocci A, Lanti A, Pescador L, Blandino F, Papetti C. Amphotericin B prophylaxis against invasive fungal infections in neutropenic patients: A single center experience from 1980 to 1995. *Infection.* 1996;24(5):361-366.

102. Dekker AW, Verdonck LF, Rozenberg-Arska M. Infection prevention in autologous bone marrow transplantation and the role of protective isolation. *Bone Marrow Transplantation.* 1994;14(1):89-93.

103. Ezdinli EZ, O'Sullivan DD, Wasser LP, Kim U, Stutzman L. Oral amphotericin for candidiasis in patients with hematologic neoplasms. An autopsy study. *JAMA.* 1979;242(3):258-260.

104. Fukushima C, Matsuse H, Tomari S, et al. Oral candidiasis associated with inhaled corticosteroid use: Comparison of fluticasone and beclomethasone. *Annals of Allergy, Asthma and Immunology.* 2003;90(6):646-651.

105. Hoppe JE, Klausner M, Klingebiel T, Niethammer D. Retrospective analysis of yeast colonization and infections in paediatric bone marrow transplant recipients. *Mycoses.* 1997;40(1-2):47-54.

106. Jurkunas U, Behlau I, Colby K. Fungal keratitis: Changing pathogens and risk factors. *Cornea.* 2009;28(6):638-643.

107. Kataoka-Nishimura S, Akiyama H, Saku K, et al. Invasive infection due to Trichosporon cutaneum in patients with hematologic malignancies. *Cancer.* 1998;82(3):484-487.

108. Kozinn PJ, Taschdjian CL, Dragutsky D, Minsky A. Treatment of cutaneous candidiasis in infancy and childhood with nystatin and amphotericin B. *Antibiotics annual.*128-134.

109. Schauwvlieghe AFAD, de Jonge N, van Dijk K, et al. The diagnosis and treatment of invasive aspergillosis in Dutch haematology units facing a rapidly increasing prevalence of azole-resistance. A nationwide survey and rationale for the DB-MSG 002 study protocol. *Mycoses.* 2018;61(9):656-664.

110. Monod M, Mehul B. Recent Findings in Onychomycosis and Their Application for Appropriate Treatment. *J Fungi (Basel).* 2019;5(1).

111. Lurati M, Baudraz-Rosselet F, Vernez M, et al. Efficacious treatment of non-dermatophyte mould onychomycosis with topical amphotericin B. *Dermatology.* 2011;223(4):289-292.

*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 **amphotericin B.** 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: Amphotericin B**

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

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

*Display This Question:*

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

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

*Display This Question:*

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

Q4. Please list all combination products in which you use compounded **amphotericin B.**

________________________________________________________________

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

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

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

________________________________________________________________

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

- ○ Yes
- ○ No

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

*Display This Question:*

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

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

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

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

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

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

**End of Block: Amphotericin B**

**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**