

Summary Report

Pitcher Plant

Prepared for:

Food and Drug Administration

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

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REVIEW OF NOMINATION

Pitcher plant (UNII code: FOP08H143P) was nominated for inclusion on the 503B Bulks List by High Chemical Company to treat chronic pain syndromes for temporomandibular joint (TMJ) use, migraine cephalgia, interdigital neuromas, omohyoideus myofascial pain syndrome, neuralgia (intercostal, branchial plexus, lumbar, and trigeminal), alcoholic neuritis, occipital neuritis, meralgia paresthetica, and sciatic pain.

Pitcher plant will be compounded as a 0.17 g/mL solution for injection that will contain no bacteriostatic agents, antimicrobial agents, or added buffers.

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

- The sterile solution of *Sarracenia purpurea* (pitcher plant) is a natural product. There are no similar natural FDA-approved products available.
- Pitcher plant helps reduce inflammation and reliance on steroids without affecting the glucose levels in the blood.
- In over 75 years, no known adverse reactions have been reported, and its use for pain relief has not been shown to cause any motor weakness or loss of touch, pressure, pin-prick, or temperature sensibility.
- The half-life of lidocaine and bupivacaine is substantially shorter than the pitcher plant sterile solution. Therefore, they are inadequate as replacements to the longer-acting pitcher plant sterile solution.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of pitcher plant 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 pitcher plant; name variations of pitcher plant 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 pitcher plant. 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 20, 2019. The search included a combination of ("pitcher plant"[TIAB] OR sarapin[TIAB] OR Sarracenia*[TIAB]) AND (clinical[TIAB] OR treat*[TIAB] OR thera*[TIAB] OR pain[TIAB] OR numb*[TIAB] OR neck[TIAB] OR neuralgia[TIAB] OR inflammation[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. Articles were considered relevant based on the identification of a clinical use of pitcher plant or the implementation of pitcher plant 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.

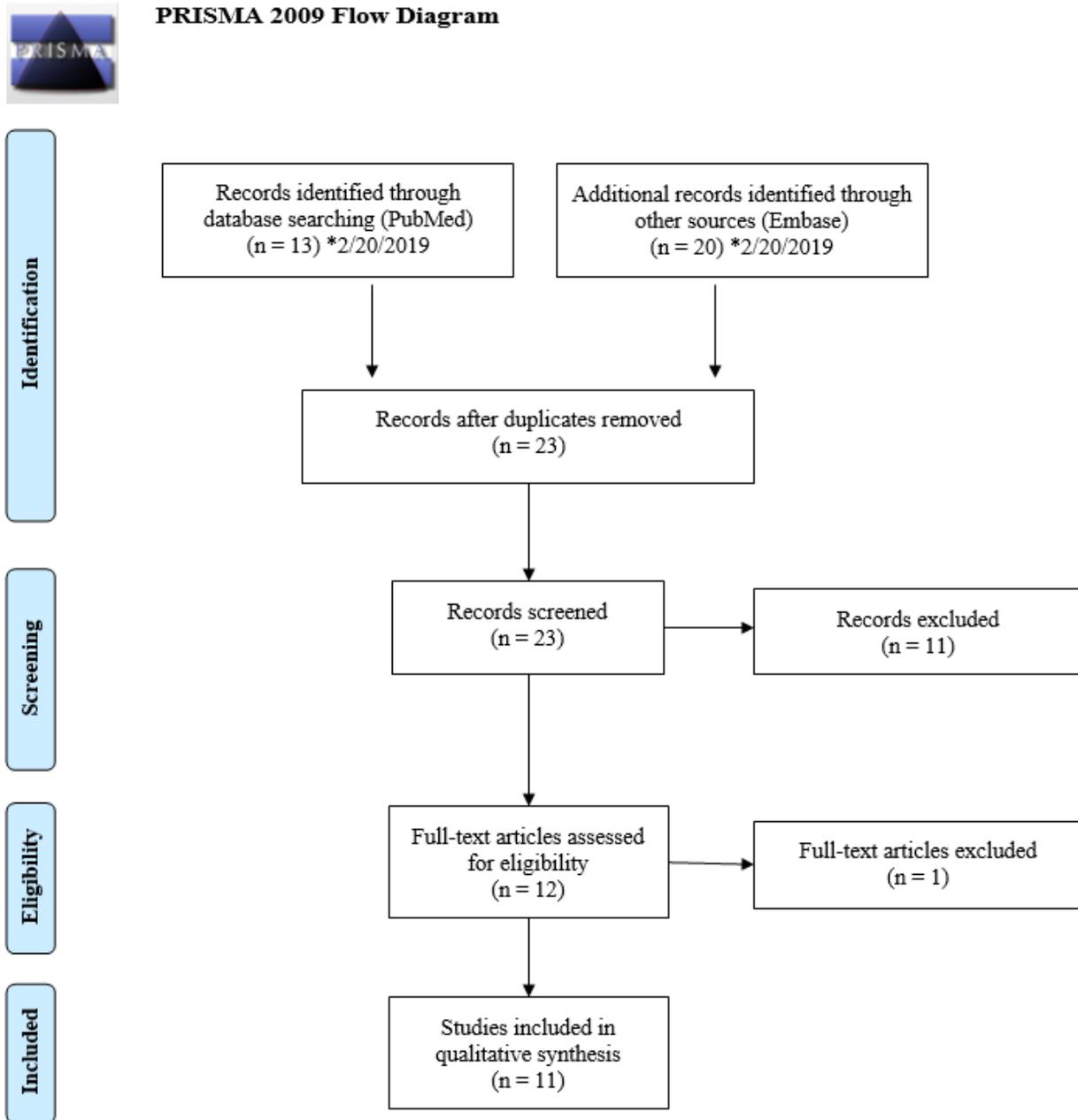
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for pitcher plant 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 pitcher plant compared to alternative therapies.

Results

Please refer to Figure 1.

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



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

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

Outreach to medical specialists and specialty organizations

Using the indications from the nomination and the results of the literature review, three (3) medical specialties that would potentially use pitcher plant were identified: naturopathy, neurology, and pain management. One (1) medical expert specializing in neurology failed to respond to the interview request. No interviews were conducted.

Survey

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

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to six (6) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

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

Table 1. Participating associations

| Specialty | Association |
|------------------|--|
| Naturopathy | American Association of Naturopathic Physicians (AANP) |
| Pain Medicine | American Academy of Pain Medicine (AAPM) |
| Primary Care | American Academy of Environmental Medicine |

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 |
| Neurology | American Academy of Neurology (AAN) | Failed to respond |

CURRENT AND HISTORIC USE

Summary of background information

- Pitcher plant is not available as an FDA-approved product.
- Pitcher plant is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for pitcher plant.
- Pitcher plant is available in Canada (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 |
| Pitcher plant | 100% | Solution | Intramuscular | Canada | Ethical | 12/31/1942 |

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

^aMedicine 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.

Summary of literature review

- One (1) of the studies mentions that pitcher plant, Sarapin, went onto the market prior to 1938. It was “grandfathered” and did not get evaluated by the FDA.³
- Total number of studies included: 11 studies (3 descriptive, 7 experimental, and 1 observational).
- All of the studies were from the US.
- The most common indications for the use of pitcher plant were for back and neck pain.
- No compounded products were identified from any studies.

Table 5. Types of studies

| Types of Studies | Number of Studies |
|------------------------------|--------------------------|
| Descriptive ¹⁻³ | 3 |
| Experimental ⁴⁻¹⁰ | 7 |
| Observational ¹¹ | 1 |

Table 6. Number of studies by country

| Country | Number of Studies |
|---------------------------|--------------------------|
| US ¹⁻¹¹ | 11 |
| Total US: 11 | |
| Total non-US Countries: 0 | |

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 |
|--|------|---------------|---------------------|-------------|-----------------------|
| Back pain ^{1,4,6-10} | – | – | Injection, solution | – | Once-Twice |
| | | | | Intracaudal | |
| Neck pain ^{1,4,5} | – | – | Injection, solution | – | Once-Twice |
| Facet arthropathy ¹¹ | 1mL | – | Injection | – | – |
| Lower right quadrant abdominal pain ³ | 10mL | – | Solution | Intrathecal | – |
| Sciatic pain ² | 1mL | – | Injection | – | – |

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

Table 9. Dosage by indication – non-US countries

No studies identified in non-US countries

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

No interviews were conducted.

Table 12. Overview of interviewees

No interviews were conducted

Summary of survey results

Table 13. Characteristics of survey respondents [12 people responded to the survey^a]

| Board Certification | MD | ND | No Response |
|---|-----------|-----------|--------------------|
| Anesthesiology | 1 | 0 | 0 |
| Fellow of the American Board of Naturopathic Oncology | 0 | 1 | 0 |
| Naturopathic Doctor | 0 | 3 | 0 |
| Naturopathic Physician | 0 | 3 | 0 |
| Neurology | 1 | 0 | 0 |
| Pain Medicine | 3 | 0 | 0 |
| No Response | 0 | 0 | 5 |

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

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

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

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

^aOut of 12 respondents, one (1) reported using, prescribing, or recommending pitcher plant products.

Table 15. Compounded use of pitcher plant in practice^a

| Indication | Strength | Dosing Frequency | Dosage Form | ROA | Duration of Treatment | Patient Population |
|--------------------|-----------------|-------------------------|--------------------|------------|------------------------------|---------------------------|
| Pain, inflammation | – | – | – | – | – | – |

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

^aOne (1) respondent.

Table 16. Indications for which pitcher plant is considered a standard therapy

| Indication | Standard Therapy | |
|--------------------|---------------------|-------------------------|
| | Compounded, n (N=1) | Non-compounded, n (N=0) |
| Pain, inflammation | 1 | 0 |

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

| Reasons |
|----------|
| “better” |

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

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

^aOne (1) respondent wrote “add to prolo [sic] treatments!!”.

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

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

^aRespondent reports stocking non-patient-specific compounded pitcher plant obtained from a compounding pharmacy in a physician office for convenience.

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

No additional survey respondents provided this information

CONCLUSION

Pitcher plant (UNII code: FOP08H143P) was nominated for inclusion on the 503B Bulks List for multiple pain and neurological indications as a 0.17 g/mL solution for injection that will contain no bacteriostatic agents, antimicrobial agents, or added buffers.

Pitcher plant is not available as an FDA-approved product, but is approved in Canada.

From the literature review, all of the studies were from the US and the most common indications were back and neck pain. No compounded products were identified from any studies. One (1) of the studies mentions that pitcher plant, Sarapin, went onto the market prior to 1938.³ It was “grandfathered” and did not get evaluated by the FDA.³

One (1) medical expert specializing in neurology failed to respond to the interview request. No interviews were conducted.

From the survey responses, one (1) out of 12 respondents used pitcher plant. The respondent who reported using compounded pitcher plant uses it for pain and inflammation and purchases non-patient-specific compounded pitcher plant from a compounding pharmacy for convenience to stock in the physician office.

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 **pitcher plant**. 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: Pitcher plant

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

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

Display This Question:

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

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

Display This Question:

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

Q4. Please list all combination products in which you use compounded **pitcher plant**.

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

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

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

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

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

End of Block: Pitcher plant

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