Summary Report

# Carbamazepine

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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# Frequently Used Abbreviations

| | |
|---|---|
| API | Active Pharmaceutical Ingredient |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| IRB | Institutional Review Board |
| OTC | Over-the-counter |
| ROA | Route of administration |
| SME | Subject matter expert |
| UK | United Kingdom |
| US | United States |

## INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of carbamazepine (UNII code: 33CM23913M), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how carbamazepine is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how carbamazepine has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of carbamazepine and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

## REVIEW OF NOMINATION

Carbamazepine was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc.

Carbamazepine was nominated for the treatment of chronic neuropathic pain via topical and mucosal dosage forms (creams, ointments, gels, and pastes) in various strengths ranging from 1-10%.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of carbamazepine.[6-11]

The reason provided for nomination to the 503B Bulks List is that excipients from carbamazepine tablets are not acceptable additives for compounded topical and mucosal preparations.

## METHODOLOGY

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of carbamazepine 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 carbamazepine; name variations of carbamazepine 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 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing carbamazepine. 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

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: carbamazepine, topical or mucosal administration, and therapeutic use for neuropathic pain (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on April 3, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 3, 2020 for clinical practice guidelines that recommended the use of carbamazepine and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which carbamazepine was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if carbamazepine was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which carbamazepine was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of carbamazepine; setting; total number of patients; number of patients who received carbamazepine; patient population; indication for use of carbamazepine; dosage form and strength; dose; ROA; frequency and duration of therapy; use of carbamazepine in a combination product; use and formulation of carbamazepine in a compounded product; use of carbamazepine compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

*Interviews*

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances carbamazepine was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use carbamazepine: endocrinology, neurology, and pain management. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

*Survey*

A survey was distributed to the members of professional medical associations to determine the use of carbamazepine in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched 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 email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

## CURRENT AND HISTORIC USE

*Results of background information*

- Carbamazepine is not available as an FDA-approved product in the nominated dosage form and ROA.
- Carbamazepine is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for carbamazepine.
- Carbamazepine is not available in the nominated dosage form and ROA in any of the national medical registries searched.

Table 1. Currently approved products – US

*No approved products in the US*

Table 2. Currently approved products – select non-US countries and regions

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

*Results of literature review*

## Study selection

Database searches yielded 836 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 644 titles and abstracts were screened. After screening, the full text of 100 articles was reviewed. Finally, 0 studies were included. The 100 studies were excluded for the following reasons: wrong study design (83 studies); wrong dosage form or ROA (6); wrong indication (4); carbamazepine only mentioned briefly (3); unable to obtain full text (2); carbamazepine not used clinically (1); wrong substance (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

## Characteristics of included studies

No studies were included from the literature review.

## Use of carbamazepine

No studies were included from the literature review.

## Pharmacology and historical use

Eleven studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of carbamazepine.

The anticonvulsant carbamazepine has a history of being used to treat pain; it is used for treating trigeminal neuralgia, and "controlled studies also have shown that carbamazepine is effective in diabetic neuropathy, migraine prophylaxis, central pain after stroke, and postherpetic neuralgia."[12]

Trigeminal neuralgia is defined by the International Association for the Study of Pain (IASP) as "sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve."[13] Trigeminal neuralgia is also referred to as "tic douloureux" or the "suicide disease" due to its severity and morbidity.[14,15] According to the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS), carbamazepine was first used to treat trigeminal neuralgia in the 1960s; before the introduction of carbamazepine (and phenytoin in the 1940s), the management of trigeminal neuralgia was surgical.[13] The 2008 guidelines from the AAN and the EFNS on trigeminal neuralgia management described 4 placebo-controlled studies in which 147 patients experienced pain relief with carbamazepine treatment (200-1200 mg/day); the ROA was not specified.[13] However, oxcarbazepine is often used as initial treatment for trigeminal neuralgia for reasons "mainly related to its documented efficacy in epilepsy and accepted greater tolerability and decreased potential for drug interactions" when compared to carbamazepine.[13] However, in a 2019 review, carbamazepine was still considered the most effective treatment for trigeminal neuralgia, along with the better tolerated oxcarbazepine.[16] Carbamazepine has also been used to confirm the diagnosis of trigeminal neuralgia, "as other types of facial pain do not respond to the drug."[17]

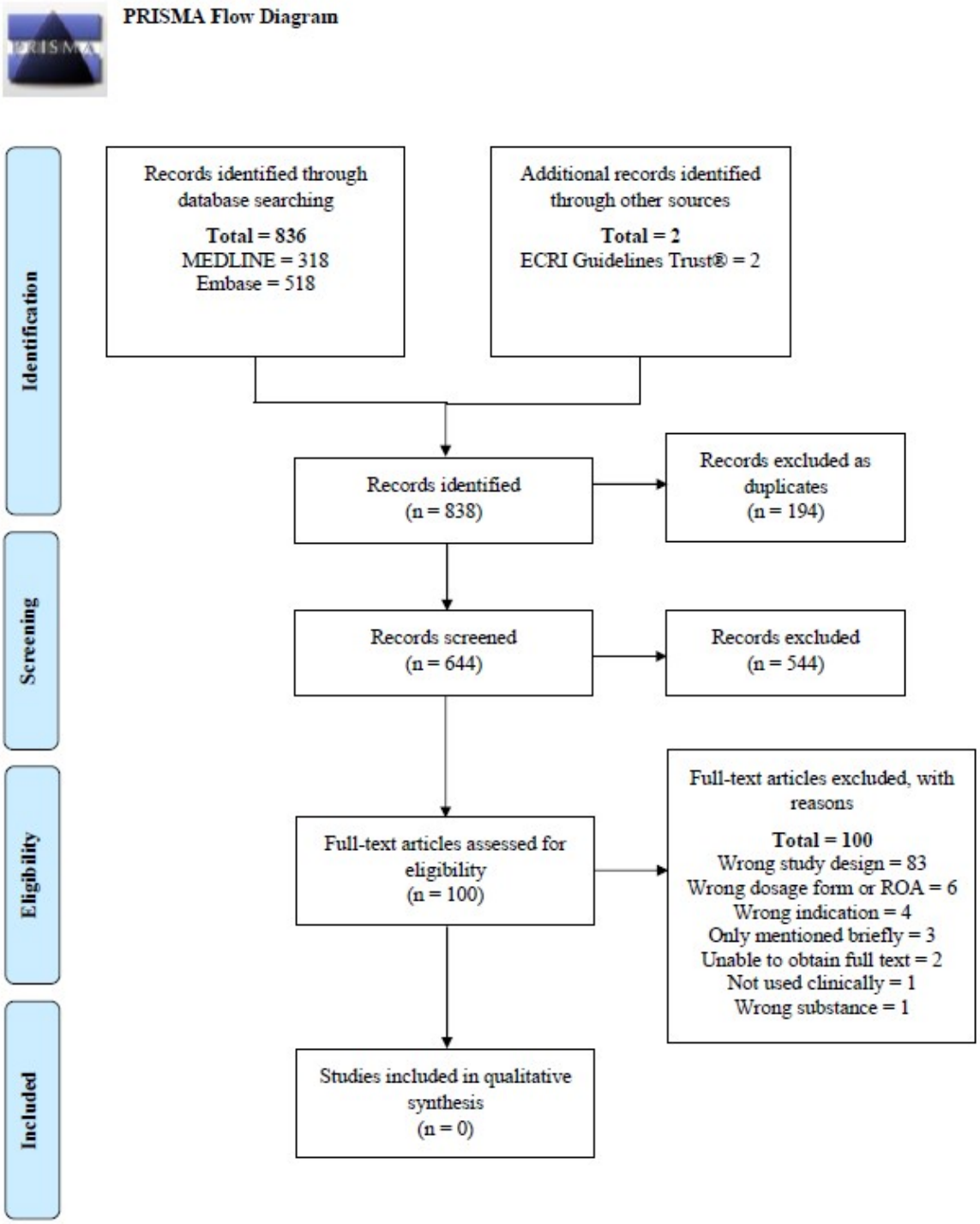
Carbamazepine was also mentioned in a review of the management of painful diabetic neuropathy.[18] The authors of this review stated that the trials on the use of carbamazepine for diabetic neuropathy "were small and some conflicting evidence was found. Larger studies would be helpful to determine the role of these agents in the treatment of peripheral diabetic neuropathy."[18] Regardless, in a 2011

review discussing pharmacological options to treat diabetic neuropathic pain, carbamazepine was listed amongst the second-tier agents for painful diabetic neuropathy.[19] Another review commented that the target carbamazepine dose for neuropathic pain in clinical practice is 1000-1500 mg/day, with patients starting at 200 mg/day and increasing at a rate of 200 mg/week.[20]

More recently, a German group wrote a review on myalgia in myositis and myopathies.[21] The authors stated that myalgia is a common symptom for neuromuscular diseases such as myositis, myotonia, and hereditary myopathies and that "symptomatic treatment with mexiletine or carbamazepine can alleviate myotonia."[21]

While there were no studies included involving the topical use of carbamazepine as a solo product, a formula for carbamazepine topical gel, cream, or ointment for the treatment of neuropathic pain was published in the *International Journal of Pharmaceutical Compounding*.[22] Carbamazepine was the sole active ingredient in this formula.[22] No information was provided about the effectiveness of these preparations.[22] A case report was also identified that utilized a compounded gel consisting of carbamazepine 4%, lidocaine 1%, ketoprofen 4%, and gabapentin 4% in a pluronic lecithin organogel and an anhydrous base delivered via an intraoral stent for the treatment of neuropathic orofacial pain.[23] The authors concluded that while the delivery of topical medication via an intraoral stent is not common among dental practitioners, it should be encouraged for the treatment of neuropathic orofacial pain, but further research needed to be done.[23]

Figure 1. PRISMA flow diagram showing literature screening and selection.




Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

*No studies included*

Table 4. Number of studies by country

*No studies included*

Table 5. Summary of included studies

*No studies included*

Table 6. Dosage by indication – US

*No studies included*

Table 7. Dosage by indication – non-US countries

*No studies included*

Table 8. Number of studies by combination

*No combination products were nominated*

Table 9. Compounded products – US

*No studies included*

Table 10. Compounded products – non-US countries

*No studies included*

*Results of interviews*

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Eight SMEs discussed carbamazepine. Amongst the 8 SMEs, there were 1 medical doctor, 1 nurse practitioner, 2 physician assistants, 1 pharmacist, and 3 dentists. The SMEs specialized and/or were board-certified in anesthesiology, dentistry, oncology, oral and maxillofacial surgery, pain medicine and palliative care, working in academic medical centers and physician's offices/private practice. The SMEs had been in practice for 5 to 25 years.

Tegretol® (carbamazepine) is an anticonvulsant that is used for seizures but also has a history of being used for patients with refractory neuropathic pain conditions (such as trigeminal neuralgia or chronic facial pain) that did not respond to other oral medications such as Tylenol® (acetaminophen), Advil® (ibuprofen), or tramadol. One SME said that it is typically administered as an oral product, and it is considered first-line for trigeminal neuralgia. When asked about the possibility of carbamazepine being used as a topical product, responses varied. One SME suggested that a carbamazepine gel would decrease the systemic absorption of the drug, resulting in lower incidence of liver issues amongst other side effects associated with long-term use. However, another SME said that they would be more concerned about side effects due to variation in patient application with topical products, especially blood dyscrasias such as anemia or agranulocytosis, "If someone slathers it on, I don't know what the absorption is. But I know with orally, they have to get their therapeutic levels checked. So, anything that may require me to monitor, I wouldn't want to use it." One SME said that patients with peripheral neuropathy often experience more benefit with topical medications instead of oral but did not comment specifically on the use of topical carbamazepine.

There were also SMEs who have heard of carbamazepine being used for pain, but they had not used it themselves. Some SMEs reported that they were familiar with carbamazepine as an anticonvulsant, along with other conditions that were not specified in the interview but were unfamiliar with its use in pain. Other SMEs said that they do not use topical carbamazepine; one said that they use benzocaine if they need a topical medication.

*Results of survey*

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

The survey respondent did not prescribe or administer carbamazepine to their patients.

Table 11. Characteristics of survey respondents

| Terminal Clinical Degree | Respondents, n (N=1) |
|---|---|
| Doctor of Medicine (MD) | 0 |
| Doctor of Osteopathic Medicine (DO) | 0 |
| Doctor of Medicine in Dentistry (DMD/DDS) | 0 |
| Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm) | 0 |
| Naturopathic Doctor (ND) | 0 |
| Nurse Practitioner (NP) | 1 |
| Physician Assistant (PA) | 0 |
| **Practice Setting** | **Respondents, n (N=1)** |
| Physician office or private practice | 0 |
| Outpatient clinic | 0 |
| Hospital or health system | 0 |
| Academic medical center | 0 |
| Emergency room | 0 |
| Operating room | 1 |

Table 12. Conditions for which carbamazepine prescribed or administered

*No survey respondents provided this information*

Table 13. Reasons for using compounded carbamazepine

*No survey respondents provided this information*

Table 14. Use of non-patient specific compounded carbamazepine

*No survey respondents provided this information*

## CONCLUSION

Carbamazepine was nominated for inclusion on the 503B Bulks List for the treatment of chronic neuropathic pain via topical and mucosal dosage forms. Carbamazepine is not approved in any of the national medical registries searched in the nominated dosage form and ROA.

From the literature review and interviews, oral carbamazepine has a history of being used for neuropathic pain, with controlled studies showing use in trigeminal neuralgia, diabetic neuropathy, migraine prophylaxis, central pain after stroke, and postherpetic neuralgia. In the studies reviewed, carbamazepine was used via the oral ROA or the ROA was not specified. The literature reviewed included a formula for a topical carbamazepine gel, cream, or ointment with the intent of being used for neuropathic pain. In addition, there was a case report where carbamazepine was used in combination with other pain medications to form a topical gel for the treatment of neuropathic orofacial pain. While SMEs were familiar with the use of oral carbamazepine for pain, they differed in opinion on the benefit and utility of a topical dosage form. One opinion was that since topical pain medications work well with patients with peripheral neuropathy, they could see the utility in compounding carbamazepine into a topical form. They also said that they could see a topical route decreasing the systemic absorption of the drug, and potentially resulting in fewer side effects. An opposing thought was that they would be more concerned about side effects, since there would be less control over how much a patient might apply, requiring close lab monitoring. Furthermore, one SME said that they would not use topical carbamazepine as they have benzocaine if they want a topical option.

From the survey responses, the one survey respondent did not use compounded carbamazepine.

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## APPENDICES

*Appendix 1. Search strategies for bibliographic databases*

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to April 2, 2020
- Date last searched: April 3, 2020
- Limits: Humans (search hedge); English language
- Number of results: 318

| | | |
|---|---|---|
| 1 | carbamazepine/ | 11036 |
| 2 | carbamazep#n$.tw. | 14898 |
| 3 | or/1-2 | 17814 |
| 4 | exp administration, topical/ | 86701 |
| 5 | topical$.tw. | 103211 |
| 6 | percutaneous$.tw. | 141779 |
| 7 | cutaneous$.tw. | 148965 |
| 8 | transdermal$.tw. | 14292 |
| 9 | derm$.tw. | 237893 |
| 10 | mucosal$.tw. | 118199 |
| 11 | mucous$.tw. | 22638 |
| 12 | emulsions/ | 17698 |
| 13 | exp gels/ | 50848 |
| 14 | liniments/ | 122 |
| 15 | ointments/ | 12745 |
| 16 | skin cream/ | 983 |
| 17 | emulsion?.tw. | 32198 |
| 18 | gel?.tw. | 304365 |
| 19 | liniment?.tw. | 143 |
| 20 | ointment?.tw. | 11674 |

| | | |
|---|---|---|
| 21 | salve?.tw. | 339 |
| 22 | paste?.tw. | 12180 |
| 23 | unguent$.tw. | 112 |
| 24 | lotion?.tw. | 2264 |
| 25 | cream?.tw. | 18547 |
| 26 | or/4-25 | 1138904 |
| 27 | exp pain/ | 390362 |
| 28 | exp neuralgia/ | 20102 |
| 29 | restless legs syndrome/ | 3645 |
| 30 | pain management/ | 33066 |
| 31 | ad.fs. | 1397567 |
| 32 | dt.fs. | 2191687 |
| 33 | tu.fs. | 2197305 |
| 34 | pc.fs. | 1267953 |
| 35 | analges$.tw. | 121095 |
| 36 | pain$.tw. | 677433 |
| 37 | neuropath$.tw. | 129255 |
| 38 | neuralg$.tw. | 13321 |
| 39 | neurodyn$.tw. | 797 |
| 40 | (restless adj2 (arm? or leg?)).tw. | 4659 |
| 41 | anxietas tibiarum.tw. | 4 |
| 42 | ekbom.tw. | 220 |
| 43 | or/27-42 | 5189087 |
| 44 | and/3,26,43 | 395 |
| 45 | exp animals/ not humans/ | 4685426 |
| 46 | 44 not 45 | 367 |

| | | |
|---|---|---|
| 47 | limit 46 to english language | 318 |

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 3, 2020
- Limits: Humans (search hedge); English language
- Number of results: 518

| | | |
|---|---|---|
| 1 | carbamazepine'/mj | 17337 |
| 2 | carbamazepen*':ti,ab,tn | 2 |
| 3 | carbamazepin*':ti,ab,tn | 21192 |
| 4 | #1 OR #2 OR #3 | 28186 |
| 5 | topical drug administration'/exp | 110875 |
| 6 | topical*':ti,ab | 146551 |
| 7 | cutaneous*':ti,ab | 213888 |
| 8 | transdermal*':ti,ab | 20862 |
| 9 | derm*':ti,ab | 372911 |
| 10 | mucosal*':ti,ab | 168203 |
| 11 | mucous*':ti,ab | 38233 |
| 12 | cream'/de | 9199 |
| 13 | gel'/exp | 73793 |
| 14 | liniment'/de | 248 |
| 15 | lotion'/de | 2809 |
| 16 | ointment'/exp | 18393 |
| 17 | paste'/de | 2490 |
| 18 | salve'/de | 165 |
| 19 | emulsion'/exp | 44326 |
| 20 | cream$':ti,ab | 29067 |
| 21 | emulsion$':ti,ab | 44030 |
| 22 | lotion$':ti,ab | 3944 |

| | | |
|---|---|---|
| 23 | ointment$':ti,ab | 21305 |
| 24 | paste$':ti,ab | 14662 |
| 25 | salve$':ti,ab | 470 |
| 26 | suppositor*':ti,ab | 7080 |
| 27 | unguent*':ti,ab | 239 |
| 28 | liniment*':ti,ab | 239 |
| 29 | gel$':ti,ab | 357824 |
| 30 | #5 OR #6 OR #7 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 | 1391737 |
| 31 | topical treatment'/de | 12459 |
| 32 | pain'/exp | 1366244 |
| 33 | neuralgia'/exp | 114230 |
| 34 | restless legs syndrome'/de | 9935 |
| 35 | analgesia'/de | 126462 |
| 36 | drug dose':lnk | 622444 |
| 37 | drug administration':lnk | 1724613 |
| 38 | drug therapy':lnk | 3857013 |
| 39 | prevention':lnk | 1162442 |
| 40 | analges*':ti,ab | 178409 |
| 41 | pain*':ti,ab | 1039328 |
| 42 | neuropath*':ti,ab | 191446 |
| 43 | neuralg*':ti,ab | 19995 |
| 44 | neurodyn*':ti,ab | 1085 |
| 45 | (restless NEAR/2 (arm$ OR leg$)):ti,ab | 7763 |
| 46 | anxietas tibiarum':ti,ab | 6 |
| 47 | ekbom':ti,ab | 459 |

| | | |
|---|---|---|
| 48 | #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 | 6405946 |
| 49 | #4 AND #30 AND #48 | 647 |
| 50 | [animals]/lim NOT [humans]/lim | 6013076 |
| 51 | #49 NOT #50 | 614 |
| 52 | #49 NOT #50 AND [english]/lim | 518 |

*Appendix 2. Survey instrument*

Welcome. We want to understand your clinical use of compounded carbamazepine. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this 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.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

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.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

| | Very familiar | Somewhat familiar | Not familiar |
|---|---|---|---|
| Compounded drugs (medications prepared to meet a patient-specific need) | o | o | o |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | o | o | o |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | o | o | o |

2. Do you prescribe or administer carbamazepine to your patients?

    - o Yes
    - o No

3. Do you prescribe or administer carbamazepine by any of the following dosage forms and/or routes of administration? (check all that apply)

    - o Topical or mucosal cream
    - o Topical or mucosal ointment
    - o Topical or mucosal gel
    - o Topical or mucosal paste
    - o None of the above

4. I prescribe or administer carbamazepine for the following conditions or diseases: (check all that apply)

    - o Chronic neuropathic pain
    - o Other (please explain) _____

5. I use compounded carbamazepine because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain)_____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing carbamazepine.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded carbamazepine at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded carbamazepine from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

   - o Physician office/private practice
   - o Outpatient clinic
   - o Hospital/health system
   - o Academic medical center
   - o Emergency room
   - o Operating room
   - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

   - o Doctor of Medicine (MD)
   - o Doctor of Osteopathic Medicine (DO)
   - o Doctor of Medicine in Dentistry (DMD/DDS)
   - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
   - o Naturopathic Doctor (ND)
   - o Nurse Practitioner (NP)
   - o Physician Assistant (PA)
   - o Other (please describe) _____

*Appendix 3. Survey distribution to professional associations*

| Specialty | Association[a] | Agreed/Declined, Reason for Declining |
|---|---|---|
| Allergy/Immunology | American Academy of Allergy, Asthma, and Immunology (AAAI) | Declined – survey not approved |
| Anesthesia | American Society of Regional Anesthesia and Pain Medicine (ASRA) | Declined – failed to respond |
| | Society for Ambulatory Anesthesia (SAMBA) | Declined – failed to respond |
| | Society for Neuroscience in Anesthesiology and Critical Care | Declined – failed to respond |
| Critical Care | Critical Care Societies Collaborative | Declined – failed to respond |
| Dentistry & Oral Medicine | Academy of General Dentistry (AGD) | Declined – provided interview referrals |
| | American Dental Association (ADA) | Declined – failed to respond |
| Dermatology | American Academy of Dermatology (AAD) | Agreed |
| | American Osteopathic College of Dermatology (AOCD) | Declined – not interested |
| Endocrinology | The Endocrine Society (ENDO) | Agreed |
| | Pediatric Endocrine Society | Agreed |
| Gastroenterology | American Gastroenterological Association (AGA) | Declined – failed to respond |
| | Obesity Medicine Association (OMA) | Declined – did not have anyone to contribute to research |
| Hematology | American Society of Hematology (ASH) | Declined – does not distribute surveys |
| Infectious Disease | American Academy of HIV Medicine (AAHIVM) | Declined – failed to respond |
| Medicine | American Medical Association (AMA) | Declined – failed to respond |

| | | |
|---|---|---|
| Naturopathy | American Association of Naturopathic Physicians (AANP) | Agreed |
| | The Oncology Association of Naturopathic Physicians (OncANP) | Agreed |
| Nephrology | American College of Clinical Pharmacists: Nephrology Practice Network | Agreed |
| | American Society of Nephrology | Declined – provided interview referrals |
| Nutrition | American Society for Parenteral and Enteral Nutrition (ASPEN) | Declined – provided interview referrals |
| Obstetrics and Gynecology | American Gynecological and Obstetrical Society (AGOS) | Declined – failed to respond |
| | Nurse Practitioners in Women's Health | Agreed |
| Ophthalmology | American Academy of Ophthalmology (AAO) | Agreed |
| Otolaryngology | American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) | Declined – survey not approved |
| Pain Management | American Academy of Pain Medicine (AAPM) | Declined – survey not approved |
| | American Academy of Physical Medicine and Rehabilitation | Declined – failed to respond |
| Pediatrics and Neonatology | American Academy of Pediatrics (AAP) | Agreed |
| Primary Care | American College of Physicians (ACP) | Declined – failed to respond |
| Psychiatry | American Academy of Clinical Psychiatrists | Declined – failed to respond |
| | American Association for Geriatric Psychiatry | Declined – failed to respond |
| Rheumatology | American College of Rheumatology (ACR) | Agreed |

| | | |
|---|---|---|
| Surgery | Ambulatory Surgery Center Association (ASCA) | Agreed |
| | American Academy of Orthopaedic Surgeons (AAOS) | Declined – no interest in participation from members |
| | American Association of Hip and Knee Surgeons (AAHKS) | Declined – only send surveys from members |
| | American College of Surgeons (ACS) | Agreed |
| | American Society for Metabolic and Bariatric Surgery (AMBS) | Declined – only send surveys from members |
| | The Association of Bone and Joint Surgeons | Declined – failed to respond |
| | Physician Assistants in Orthopaedic Surgery | Declined – failed to respond |
| | Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) | Declined – failed to respond |
| | Society of Gynecologic Surgeons (SGS) | Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin |
| Toxicology | American Academy of Environmental Medicine (AAEM) | Declined – failed to respond |
| Urology | Sexual Medicine Society of North America (SMSNA) | Agreed |

[a]Associations that declined in Year 1 were not contacted in Year 2.