

# Summary Report

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## Oxymetazoline Hydrochloride

### 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 NOMINATIONS**

Oxymetazoline hydrochloride (oxymetazoline HCl; UNII code: 8VLN5B44ZY) was nominated for inclusion on the 503B Bulks List by Frier Levitt, LLC and US Compounding Pharmacy. Oxymetazoline HCl was nominated for use as an irrigation solution and then to be perfused through the joint during arthroscopic surgery to reduce postoperative inflammatory pain and improve postoperative joint motion and function as well as a musculoskeletal injection to treat acute and chronic inflammatory conditions. Oxymetazoline HCl was nominated for use in combination with other active pharmaceutical ingredients (API), refer to table 7 for the combination formulas. The reason provided for nomination to the 503B Bulks List is that there is no FDA-approved drug that provides a multi-component approach to control inflammation induced by arthroscopic surgery.

## **METHODOLOGY**

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of oxymetazoline HCl 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 oxymetazoline HCl; name variations of oxymetazoline HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing oxymetazoline HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

## *Systematic literature review*

### Search strategy

Two databases (PubMed and Embase) were searched including any date through June 18, 2019. The search included a combination of oxymetazoline[TIAB] AND (injection OR solution OR irrigation OR ketoprofen OR amitriptyline) AND (pain[TIAB] OR arthroscop\*[TIAB] OR clinic\*[TIAB] OR therap\*[TIAB] OR treat\*[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

Literature reviews and/or meta-analyses, cost-effectiveness, and epidemiological studies were excluded. Oxymetazoline HCl is a component of an FDA-approved product, as a result, articles were excluded if oxymetazoline HCl was utilized as the FDA-approved product or in the same concentration and formulation as the FDA-approved product. Articles were considered relevant based on the identification of a clinical use of oxymetazoline HCl or the implementation of oxymetazoline HCl 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.

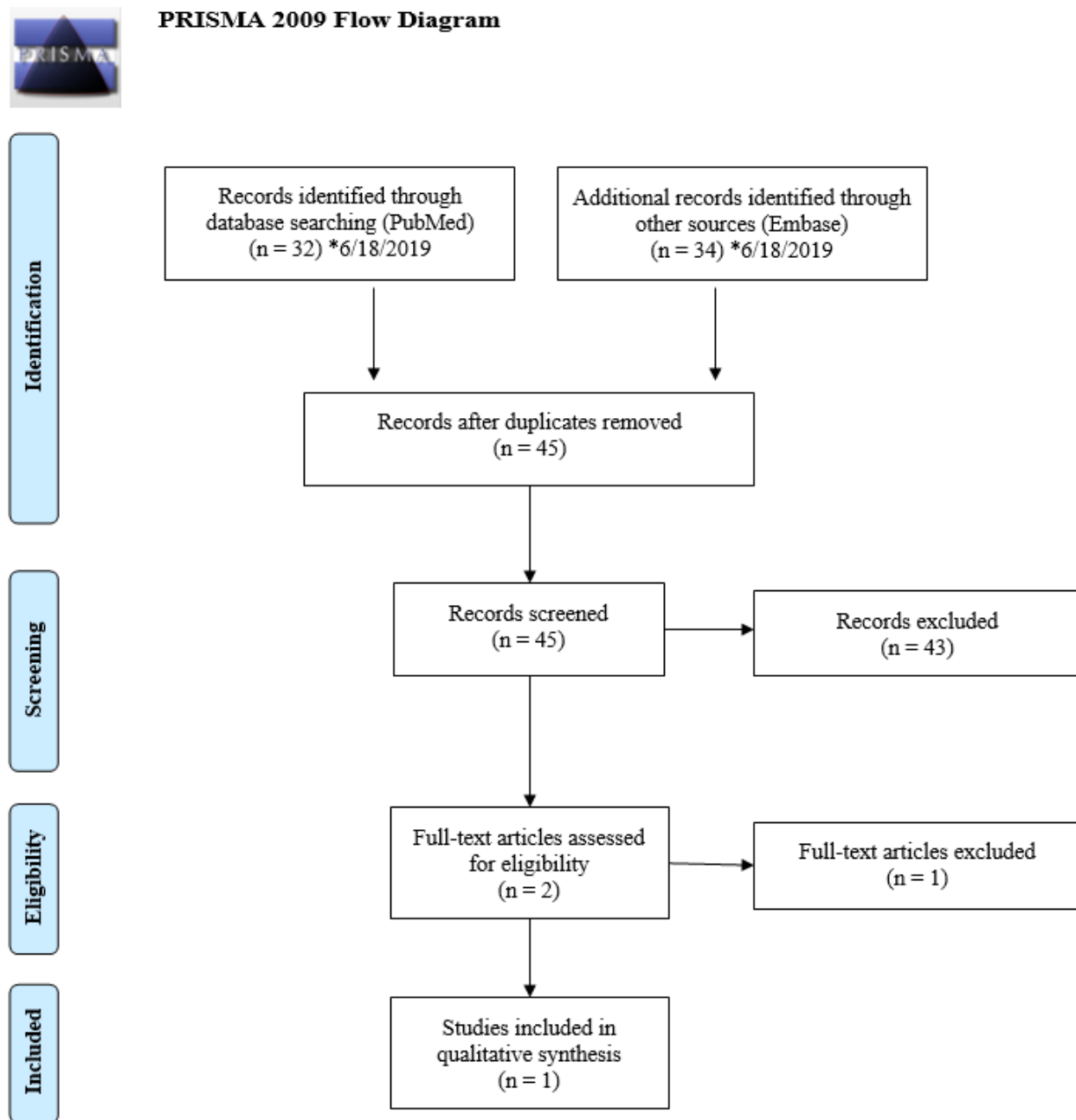
### Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for oxymetazoline HCl 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 oxymetazoline HCl 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](http://www.prisma-statement.org).

### *Outreach to medical specialists and specialty organizations*

Using the indications from the nominations and the results of the literature review, one (1) medical specialty that would potentially use oxymetazoline HCl was identified: surgery. 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. No interviews were conducted.

### *Survey*

General professional medical associations and specialty associations for surgery, identified from the nominations, 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 three (3) 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

*No associations participated*

Table 2. Associations that declined participation

<b>Specialty</b>	<b>Association</b>	<b>Reasons for Declining</b>
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Surgery	American College of Surgeons (ACS)	Failed to respond

## CURRENT AND HISTORIC USE

### *Summary of background information*

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

Table 3. Currently approved products – US

*No approved products in the US*

Table 4. Currently approved products – select non-US countries and regions

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

### *Summary of literature review*

- Only one (1) US study was included, and it utilized oxymetazoline HCl as a nominated compounded formulation.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive	0
Experimental <sup>1</sup>	1
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
US <sup>1</sup>	1
Total US: 1 Total non-US Countries: 0	



Table 7. Number of studies by combinations

	<b>Combination Formula</b>	<b>Number of Studies</b>
<b>Nominated</b>	Oxymetazoline 0.215g/L/ Ketoprofen 0.687g/L/ Amitriptyline 0.227g/L – musculoskeletal injection, surgical irrigation <sup>1</sup>	1

Table 8. Dosage by indication – US

<b>Indication</b>	<b>Dose</b>	<b>Concentration</b>	<b>Dosage Form</b>	<b>ROA</b>	<b>Duration of Treatment</b>
Antiinflammatory/analgesic <sup>1</sup>	–	–	Solution	Irrigation	during procedure

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

Table 9. Dosage by indication – non-US countries

*No studies identified*

Table 10. Compounded products – US

<b>Indication</b>	<b>Publication Year</b>	<b>Compounding Method</b>	<b>Dosage Form</b>	<b>Final Strength</b>
Antiinflammatory/analgesic <sup>1</sup>	2008	“prepared by pharmacist”	Solution	–

Abbreviation: “–”, not mentioned.

Table 11. Compounded products – non-US countries

*No compounded products from reported studies*

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

Zero (0) interviews were conducted.

Table 12. Overview of interviewee

*No interviews were conducted*

*Summary of survey results*

Table 13. Characteristics of survey respondents [1 person responded to the survey.]

<b>Board Certification</b>	<b>PhD</b>
No Board certification	1
No Response	0

Abbreviation: PhD, Doctor of Philosophy.

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

*No survey respondents provided this information*

Table 15. Compounded use of oxymetazoline HCl in practice

*No survey respondents provided this information*

Table 16. Indications for which oxymetazoline HCl is considered a standard therapy

*No survey respondents provided this information*

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

*No survey respondents provided this information*

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

*No survey respondents provided this information*

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

*No survey respondents provided this information*

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

*No survey respondents provided this information*

## **CONCLUSION**

Oxymetazoline HCl (UNII code: 8VLN5B44ZY) was nominated for inclusion on the 503B Bulks List by Frier Levitt, LLC and US Compounding Pharmacy. Oxymetazoline HCl was nominated for use in combination with other active pharmaceutical ingredients (API), refer to table 7 for the combination formulas. Oxymetazoline HCl was nominated for use as an irrigation solution and then to be perfused through the joint during arthroscopic surgery to reduce postoperative inflammatory pain and improve postoperative joint motion and function as well as a musculoskeletal injection to treat acute and chronic inflammatory conditions. Oxymetazoline HCl is not approved in any of the foreign medicine registries searched.

From the literature review conducted, only one (1) study was identified with an indication for use as an anti-inflammatory/analgesic. The study utilized oxymetazoline HCl as a compounded product in the nominated formulation. No interviews were conducted, and zero (0) out of one (1) survey respondent used oxymetazoline HCl.

## **APPENDICES**

### *Appendix 1. References*

1. Fanton GS, Dillingham MF, Wall MS, et al. Novel drug product to improve joint motion and function and reduce pain after arthroscopic anterior cruciate ligament reconstruction. *Arthrosc - J Arthrosc Relat Surg.* 2008;24(6):625-636.

## 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 **oxymetazoline HCl**. 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](mailto: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](mailto:hrpo@umaryland.edu).

### End of Block: Welcome Page

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### Start of Block: Oxymetazoline HCl

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

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

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### Display This Question:

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

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

*Display This Question:*

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

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

- Oxymetazoline HCl 0.215g/L / Ketoprofen 0.687g/L / Amitriptyline 0.227g/L
- Other (please describe) \_\_\_\_\_

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

\_\_\_\_\_

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

\_\_\_\_\_

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

\_\_\_\_\_

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

- Yes
- No

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

*Display This Question:*

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

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

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

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

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

\_\_\_\_\_

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

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End of Block: Oxymetazoline HCl

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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**