

# Summary Report

---

## Dapiprazole Hydrochloride

### Prepared for:

Food and Drug Administration

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

Grant number: 2U01FD005946

### Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)

University of Maryland School of Pharmacy

February 2020

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling \$2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

# Table of Contents

REVIEW OF NOMINATIONS .....	4
METHODOLOGY .....	4
Background information.....	4
Systematic literature review.....	5
Outreach to medical specialists and specialty organizations .....	7
Survey.....	7
CURRENT AND HISTORIC USE.....	8
Summary of background information .....	8
Summary of literature review .....	8
Summary of focus groups/interviews of medical experts and specialty organizations .....	9
Summary of survey results.....	10
CONCLUSION.....	12
APPENDICES .....	13
Appendix 1. References.....	13
Appendix 2. Survey instrument .....	14

## Table of Tables

Table 1. Participating associations.....	7
Table 2. Associations that declined participation.....	8
Table 3. Currently approved products – US.....	8
Table 4. Currently approved products – select non-US countries and regions.....	8
Table 5. Types of studies .....	8
Table 6. Number of studies by country.....	8
Table 7. Number of studies by combinations.....	8
Table 8. Dosage by indication – US.....	8
Table 9. Dosage by indication – non-US countries.....	9
Table 10. Compounded products – US.....	9
Table 11. Compounded products – non-US countries .....	9
Table 12. Overview of interviewees.....	9
Table 13. Characteristics of survey respondents.....	10
Table 14. Types of products used, prescribed, or recommended .....	10
Table 15. Compounded use of dapiprazole HCl in practice.....	10
Table 16. Indications for which dapiprazole HCl is considered a standard therapy .....	11
Table 17. Reasons for using compounded product instead of the FDA-approved products.....	11
Table 18. Change in frequency of compounded dapiprazole HCl usage over the past 5 years.....	11
Table 19. Do you stock non-patient specific compounded dapiprazole HCl in your practice?.....	11
Table 20. Questions related to stocking non-patient specific compounded dapiprazole HCl.....	11

## REVIEW OF NOMINATIONS

Dapiprazole hydrochloride (Dapiprazole HCl; UNII code: DS9UJN1I0X) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS) and Rebecca Mitchell for mydriasis via a sterile lyophilized powder reconstituted for ophthalmic topical use and an ophthalmic ointment. SSPS reported an intended strength of “0.005” while Rebecca Mitchell reported a desired concentration of 0.5%.

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

- Dapiprazole has been discontinued but many ophthalmic and optometric practitioners utilize dapiprazole to reverse dilation.
- Manufacturer backorder.
- The need for a different strength or dosage form than what is commercially available.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is more safe and efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state of the art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.

## METHODOLOGY

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of dapiprazole 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 dapiprazole HCl; name variations of dapiprazole 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; 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 dapiprazole 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 April 4, 2019. The search included a combination of dapiprazole[TIAB] AND (ophthalmic OR ophth\*) AND (treat\*[TIAB] OR therap\*[TIAB] OR clinic\*[TIAB] OR mydria\*[TIAB] OR dilat\*[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. Dapiprazole HCl is a component of an FDA-approved product that has been discontinued by the manufacturer, not for safety or efficacy reasons. As a result, articles were excluded if dapiprazole HCl 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 dapiprazole HCl or the implementation of dapiprazole 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.

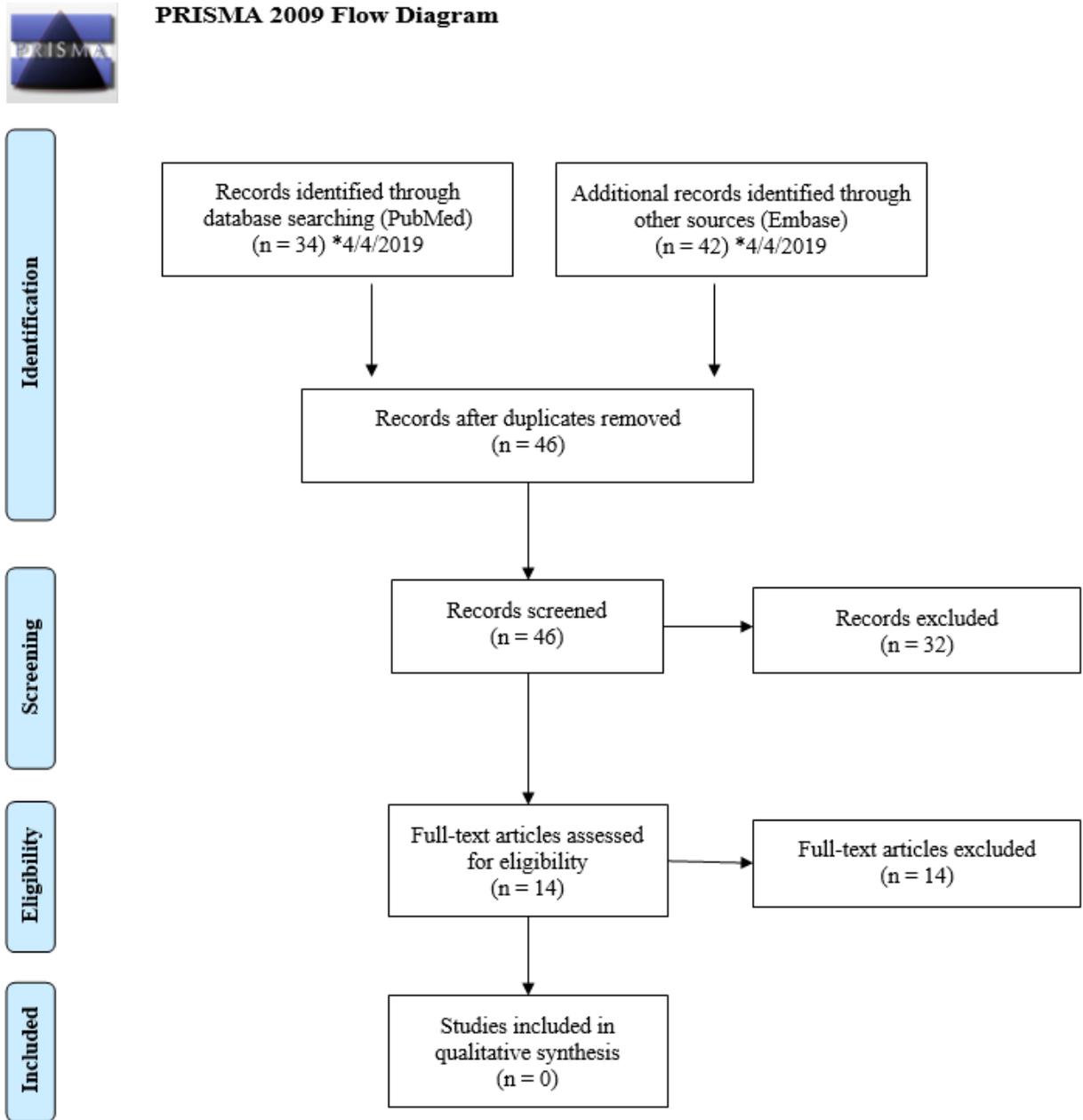
### Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for dapiprazole 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 dapiprazole 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 indication from the nominations and the results of the literature review, one (1) medical specialty that would potentially use dapiprazole was identified: ophthalmology. Semi-structured interviews were conducted with subject matter experts within this specialty. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Two (2) expert were contacted for interviews, of which two (2) accepted and zero (0) declined interviews. 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 ophthalmology, identified from the nominations, literature review, and interview, 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 five (5) 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

<b>Specialty</b>	<b>Association</b>
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

## CURRENT AND HISTORIC USE

### *Summary of background information*

- Dapiprazole HCl is not available as an FDA-approved product. Dapiprazole HCl was commercially available as a 0.5% ophthalmic solution, but this product has been discontinued.
- Dapiprazole HCl is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for dapiprazole HCl.
- Dapiprazole HCl is not available 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*

No studies identified that met the inclusion criteria.

Table 5. Types of studies

*No studies identified that met the inclusion criteria*

Table 6. Number of studies by country

*No studies identified that met the inclusion criteria*

Table 7. Number of studies by combinations

*No studies identified that met the inclusion criteria*

Table 8. Dosage by indication – US

*No studies identified that met the inclusion criteria*

Table 9. Dosage by indication – non-US countries

*No studies identified that met the inclusion criteria*

Table 10. Compounded products – US

*No studies identified that met the inclusion criteria*

Table 11. Compounded products – non-US countries

*No studies identified that met the inclusion criteria*

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

Two (2) interviews were conducted.

Table 12. Overview of interviewees

<b>Interviewee</b>	<b>Level of Training</b>	<b>Specialty</b>	<b>Current Practice Setting</b>	<b>Experience with Dapiprazole HCl</b>	<b>Interview Summary Response</b>
OPH_05	MD	Ophthalmology (retina specialist)	Academic medical institution	Not mentioned	<ul style="list-style-type: none"> <li>Remembers when dapiprazole was available, it was very expensive and had to be stored in amber bottles.</li> </ul>
OPH_08	MD	Ophthalmology (retina specialist)	Private practice	No	<ul style="list-style-type: none"> <li>Remembers that the problem with dapiprazole was that it has a harsher reversal dilation compared to the gentle wearing off of dilating drops. It could sometimes trigger angle-closure glaucoma.</li> </ul>

Abbreviation: MD, Doctor of Medicine.

*Summary of survey results*

Table 13. Characteristics of survey respondents [17 people responded to the survey]

<b>Board Certification</b>	<b>MD</b>	<b>NP</b>	<b>No Response</b>
Cardiovascular Disease	0	1	0
Ophthalmology	10	0	0
No Response	0	0	6

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner.

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

<b>Types of Products</b>	<b>Respondents, n (N=2<sup>a</sup>)</b>
Compounded	1
FDA-approved	0
Over-the-counter	0
Dietary	0
Unsure	1
No Response	0

<sup>a</sup>Out of 17 respondents, two (2) reported using, prescribing, or recommending dapiprazole HCl products.

Table 15. Compounded use of dapiprazole HCl in practice<sup>a</sup>

<b>Indication<sup>b</sup></b>	<b>Strength</b>	<b>Dosing frequency</b>	<b>Dosage Form</b>	<b>ROA</b>	<b>Duration of Treatment</b>	<b>Patient Population<sup>b</sup></b>
“Post any dilation, upon patient request”	0.5%	Once	Drops	Topical	One	“25%”

Abbreviation: ROA, route of administration.

<sup>a</sup>One (1) respondent.

<sup>b</sup>Quotations are direct words from the respondent.

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

Indication	Standard Therapy		
	Compounded, n (N=1)	Non-compounded, n (N=0)	Unsure, n (N=1)
None	1	0	0
No Response	0	0	1

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

Reasons
“Rev Eyes was discontinued”

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

	Respondents, n (N=1)
No—use has remained consistent	0
Yes—I use it LESS often now <ul style="list-style-type: none"> <li>• “Not a available”</li> </ul>	1
Yes—I use it MORE often now	0

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

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

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

*No survey respondents provided this information*

## **CONCLUSION**

Dapiprazole HCl (UNII code: DS9UJN1I0X) was nominated for inclusion on the 503B Bulks List for mydriasis via a sterile lyophilized powder reconstituted for ophthalmic topical use and an ophthalmic ointment. Dapiprazole HCl is not approved in any of the national medical registries searched. Dapiprazole HCl was available as a 0.5% ophthalmic solution, however is has been discontinued in the US, not for safety or efficacy reasons.

From the literature review, no studies were identified that met the inclusion criteria.

From the interviews, one (1) interviewee remembers dapiprazole was very expensive when it was available and does not think dapiprazole worked well. The other interviewee did not use dapiprazole before and stated that dapiprazole is a more harsh reversal dilation compared to dilating drops gently wearing off, which can sometimes trigger angle-closure glaucoma.

From the survey responses, two (2) out of 17 respondents used dapiprazole HCl. One (1) respondent reported using compounded dapiprazole HCl for post-dilation upon patient request.

## **APPENDICES**

### *Appendix 1. References*

No studies identified that met the inclusion criteria.

## 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 **dapiprazole 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

---

### Start of Block: dapiprazole HCl

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

---

### Display This Question:

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

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

*Display This Question:*

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

Q4. Please list all combination products in which you use compounded **dapiprazole HCl**.

\_\_\_\_\_

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

\_\_\_\_\_

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

\_\_\_\_\_

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

---

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

- Yes
- No

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

*Display This Question:*

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

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

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

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

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

---

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

---

**End of Block: dapiprazole HCl**

---

**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**