Summary Report

Ketoprofen

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

ACL	Anterior cruciate ligament
API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
TMJ	Temporomandibular joint
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 ketoprofen (UNII code: 90Y4QC304K), 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 ketoprofen 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 ketoprofen 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 ketoprofen 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 NOMINATIONS

Ketoprofen was nominated for inclusion on the 503B Bulks List by Fagron, Frier Levitt, and US Compounding Pharmacy. Ketoprofen was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Ketoprofen was nominated for:

- Inflammatory and dental pain via an 1-20% topical gel
- To reduce smooth muscle contraction and to inhibit inflammatory processes during and after urological procedures via a combination ketoprofen and nifedipine sterile solution that is either instilled or irrigated at the surgical site
- Joint perfusion during arthroscopic surgery to reduce postoperative inflammatory pain, and improve postoperative joint motion and function via a combination sterile solution that is either instilled or irrigated at the surgical site
- Acute and chronic inflammatory conditions via a sterile solution for musculoskeletal injection

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of ketoprofen.[6-33]

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

- As an alternative to use of opioids and narcotics
- Oral NSAIDs can lead to an increased risk of stomach ulcerations
- There is no FDA-approved drug with the ability to effectively inhibit the inflammatory and smooth muscle spasm processes
- Local delivery of ketoprofen and nifedipine to use low concentrations, reducing systemic absorption, and chance of adverse events

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ketoprofen 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 ketoprofen; name variations of ketoprofen 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 ketoprofen. 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: ketoprofen; ROA and form; and therapeutic or preventative use for pain associated with urologic or dental conditions and procedures (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 March 5, 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 March 5, 2020 for clinical practice guidelines that recommended the use of ketoprofen and provided sufficient dosing and administration instructions.

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 ketoprofen 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 ketoprofen 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 ketoprofen 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 ketoprofen; setting; total number of patients; number of patients who received ketoprofen; patient population; indication for use of ketoprofen; dosage form and strength; dose; ROA; frequency and duration of therapy; use of ketoprofen in a combination product; use and formulation of ketoprofen in a compounded product; use of ketoprofen 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 ketoprofen was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use ketoprofen: dentistry, orthopedics, rheumatology, surgery, and urology. 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 ketoprofen 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

- Ketoprofen is not available as an FDA-approved product in the nominated dosage form and ROA.
- Ketoprofen is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for ketoprofen.
- Ketoprofen is available in the nominated dosage form and ROA in Abu Dhabi, Belgium, Ireland, Latvia, Namibia, Saudi Arabia, and UK.

Table 1. Currently approved products – US

No approved products in the US

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Ketoprofen	50 mg/mL	Solution for injection	Infusion, injection, intramuscular	Belgium	Medical prescription	07/11/1985
				Hong Kong	Prescription only	11/16/2009
				Latvia	Prescription	01/20/1999
	2.5%	Gel	Cutaneous, topical, transdermal	Abu Dhabi	Active	–
				Belgium	Medical prescription	09/02/1991
				Hong Kong	Prescription only	05/22/1992
				Ireland	Prescription-only renewable	08/19/1992
				Latvia	Prescription	06/06/1996
				Namibia	–	08/18/2004
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	01/28/1993
	2.5%	Solution	Topical	Ireland	Prescription-only non-renewable	03/19/2004

Abbreviation: "– ", not mentioned.

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

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

Results of literature review

Study selection

Database searches yielded 839 references; 4 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 588 titles and abstracts were screened. After screening, the full text of 50 articles was reviewed. Finally, 8 studies were included. Forty-two (42) studies were excluded for the following reasons: wrong study design (23 studies); ketoprofen used as brand or proprietary product (8); wrong dosage form or ROA (6); ketoprofen not used clinically (2); unable to obtain full text (2); duplicate study (1).

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

Characteristics of included studies

The 8 included studies were published between 1996 and 2018. There were 8 experimental studies conducted in the following countries: Argentina, India, Iran, Japan, Turkey, UK, and US.

A total of 1960 patients participated in the 8 included studies. The number of patients in each study ranged from 10 to 1575.

Outcome measures differed among the included studies and included: pain management and relief; adverse effects secondary to study drug; probing depth; attachment level; tooth mobility; plaque index; gingival index; bleeding on probing; probing pocket depth; clinical attachment level; knee function composite; straight-leg raise.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of ketoprofen

One hundred six patients received ketoprofen as an experimental treatment for ankle sprain, administered topically as 2 g of a 2.5% gel, one time. Twenty-eight patients received ketoprofen as an experimental treatment for periodontitis, administered as a topical 1-2% gel. One thousand forty-eight patients received ketoprofen as an experimental treatment for acute soft tissue injury, administered topically as a 2.5% gel in doses ranging from 12 g/day to 15 g/day over 5 days. Fourteen patients received ketoprofen as an experimental treatment for anterior cruciate ligament (ACL) reconstruction, administered as a one-time irrigation solution in combination with amitriptyline and oxymetazoline. Twenty patients received ketoprofen as an experimental treatment for orthodontic pain, administered as a 1.6 mg/mL gel twice daily over 3 days. Forty patients received ketoprofen as an experimental treatment for total hip arthroplasty, administered as 3 periarticular analgesic injection.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Ketoprofen was used as a compounded product and was used in a combination product (refer to Tables 8 and 10).

In 7 studies, the authors' concluding statement recommended the use of ketoprofen for the treatment of ankle sprain, periodontitis, acute soft-tissue injury, ACL reconstruction, and orthodontic pain. In 1 study, the authors' concluded that further studies were necessary for the use of ketoprofen in total hip arthroplasty.

Pharmacology and historical use

In addition to the 8 included studies, 4 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of ketoprofen.

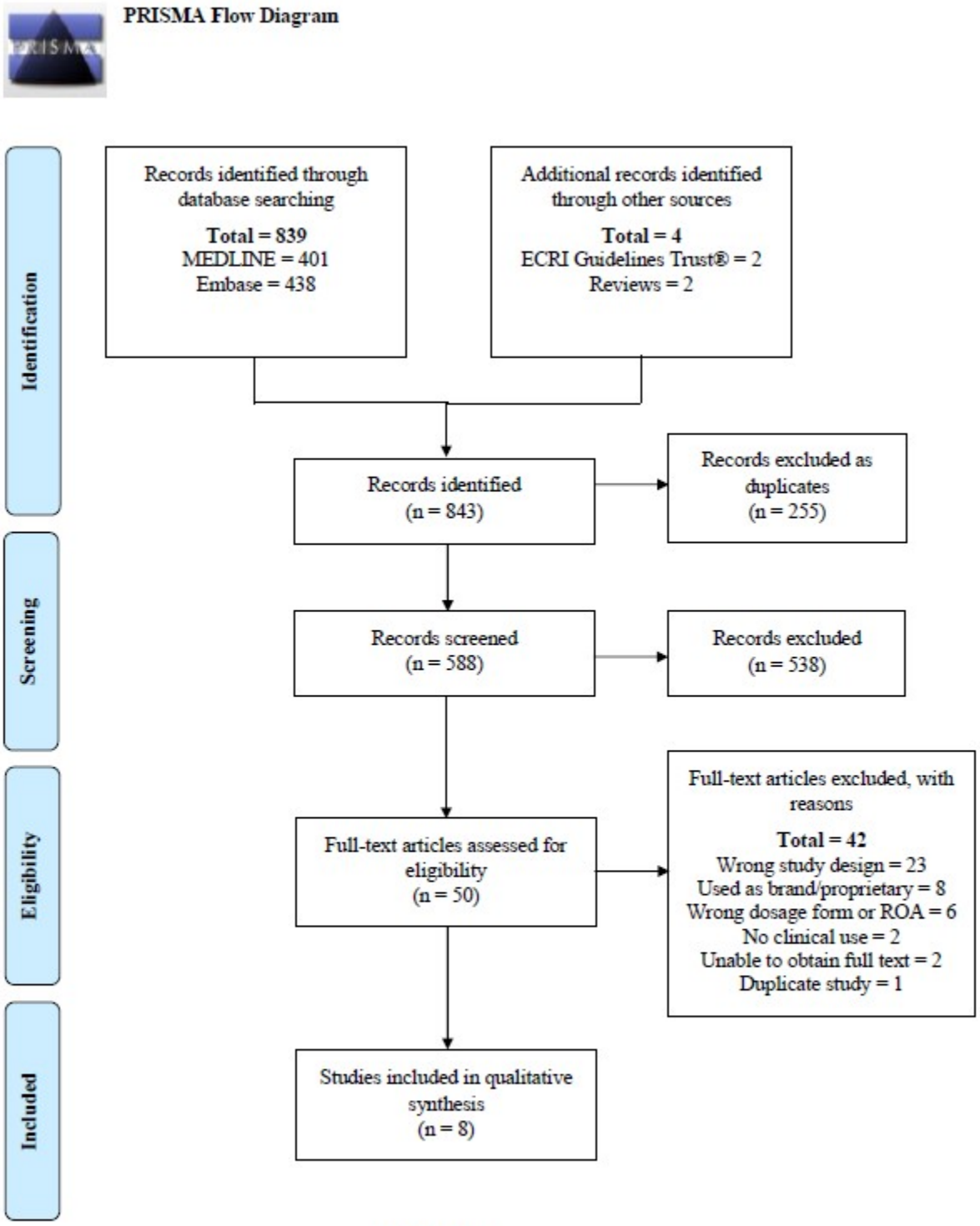
In Coaccioli's 2011 review, the author commented that guidelines produced by the European League Against Rheumatism (EULAR) and the Osteoarthritis Research Society International (OARSI) recommend using topical nonsteroidal anti-inflammatory drugs (NSAIDs) over oral NSAIDs in patients with mild to moderate knee or hand osteoarthritis.[34] The author concluded that 100-300 mg of topical ketoprofen 2.5% gel twice daily has the benefit of providing symptom relief at low plasma concentrations and a low incidence of adverse events.[34] The main indication for this topical ketoprofen gel is the local treatment of musculoskeletal pain and the inflammation of muscles and joints.[34]

However, a 2010 French commentary talks about ketoprofen gels being withdrawn from the French market in 2009 due to risk of severe cutaneous disorders.[35] However, most ketoprofen gels returned to the market within a few weeks following legal action where a manufacturer petitioned to cancel the suspended marketing authorization.[35] The judge who issued the conjunction concluded that the adverse effect was based on a small number of cases compared to the amount of ketoprofen gel sold annually. The author commented that the risk of cutaneous reactions occur with other topical NSAID-based gels, but ketoprofen has a higher risk of causing cutaneous reactions compared to ibuprofen or diclofenac.[35] In Coacicioli's review, the author comments that to reduce the risk of these cutaneous reactions, patients should avoid sun exposure and avoid application of ketoprofen gel to wounds and the eyes.[34]

In a 2018 comparison, Powell compared ketoprofen gels compounded with pure drug powder to manufactured capsules.[36] In the conclusion, the author notes that "Gels compounded with capsules were more chemically stable than gels compounded with powder. In addition, the transdermal gel compounded with capsules released in higher amounts of ketoprofen at the 24-hour time point."[36]

Micali et al studied the efficacy of nifedipine for upper-middle ureteral stones and tamsulosin for lower ureteral stones after extracorporeal shock wave lithotripsy (ESWL).[23] Nifedipine can influence the contractile activity of the ureter, and seems to be able "to inhibit the stone-induced ureteral spasm and to maintain peristaltic rhythm."[23] Both nifedipine and tamsulosin were used with ketoprofen as an anti-edema agent.[23] Nifedipine was administered at 30 mg/day orally for 14 days, tamsulosin 0.4 mg/day orally for 14 days, and ketoprofen 50 mg twice a day orally for 7 days.[23] One hundred thirteen patients were prospectively evaluated, with 35 patients given nifedipine, 28 given tamsulosin, and 50 as controls only receiving pain-relief therapy (diclofenac).[23] There was no significant difference in stone size among the groups observed. There was an 85.7% stone-free rate for the nifedipine group, 82.1% for the tamsulosin group, 51.7% for the first control group (upper-mid ureteral stones) and 57.1% for the second control group (lower ureteral stones).[23] The authors concluded that medical therapy after ESWL to help with ureteral stone expulsion resulted in an increased 1-2 months stone-free rate and lower percentage of those needing re-treatment.[23] The authors also stated that "the efficacy of nifedipine for upper-mid ureteral tract associated with [ketoprofen] makes expulsive medical therapy suitable for improving overall outcomes of ESWL treatment for ureteral stones."[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

Types of Studies	**Number of Studies**
Descriptive	0
Observational	0
Experimental[13,29,37-42]	8

Table 4. Number of studies by country

Country	**Number of Studies**
Argentina[38]	1
India[42]	1
Iran[37]	1
Japan[39]	1
Turkey[29,41]	2
UK[40]	1
US[13]	1
	Total US: 1 Total Non-US Countries: 7

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Ankle sprain					
Serinken *et al.*, 2016, Turkey[29]	Prospective randomized, double-blind controlled study	100 In-patients with lateral ankle ligament injury or medial complex injury (69%, mean 25.8 y ± 6)	• Ketoprofen (50) • Placebo (50)	Pain relief at 15 and 30 minutes after administration, need for rescue drug, and adverse effects secondary to study drug.	Ketoprofen gel was superior to placebo for ankle sprain in the emergency department (ED). Further studies are needed to evaluate long-term effects
Serinken *et al.*, 2018, Turkey[41]	Prospective randomized, double-blind study	112 In-patients with lateral ankle ligament injury or medial complex injury (60.7%, mean 12.3 y ± 2.9)	• Ketoprofen (56) • Placebo (56)	Pain relief at 15 and 30 minutes after administration, need for rescue drug, and adverse effects secondary to study drug.	Ketoprofen gel was superior to placebo for children with ankle sprains in the ED and should be considered as an option for ED physicians
Indication 2: Periodontitis					
Funosas *et al.*, 2009, Argentina[38]	Randomized clinical trial	33 Out-patients with chronic periodontitis (range 21-40 y)	• Placebo gel (6) • 1% Aspirin gel (9) • 1% Ketoprofen gel (8) • 2% Ketoprofen gel (10)	Probing depth, attachment level, tooth mobility, plaque index, gingival index, and bleeding on probing (BOP)	All protocols induced reducing of probing depths, plaque and gingival indices, and BOP. However, the 1% aspirin and 2% ketoprofen gels significantly reduced probing depth
Srinivas *et al.*, 2011, India[42]	Double-blind clinical trial	10 Out-patients with chronic periodontitis (range 33-55 y)	• Scaling and rootplaning (SRP) and ketoprofen • SRP and placebo • SRP	Plaque index, gingival index, bleeding on probing, probing pocket depth, and clinical attachment level	The combined effect of ketoprofen gel with SRP was more effective for chronic periodontitis than SRP alone
Indication 3: Acute soft-tissue injury					
Patel and Leswell, 1996, UK[40]	Open-label, comparative, parallel-group, multicenter, general practice study	1575 Out-patients with acute soft-tissue injury (60%, range 11-93 y)	• Ketoprofen gel (1048) • Piroxicam gel (263) • Diclofenac gel (264)	Physician's assessment of the response to treatment at day 5	Due to superior efficacy and patient acceptance with ketoprofen gel, it is a useful addition to established acute soft-tissue injury treatments

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 4: Anterior cruciate ligament (ACL) reconstruction					
Fanton *et al.*, 2008, US[13]	Prospective, double-blind, vehicle-controlled, parallel group, randomized study	30 In-patients for ACL reconstruction Intervention (50%, mean 31.3 y ± 7.3) Vehicle (56.3%, mean 34 y ± 6.3)	• Amitriptyline / Ketoprofen / Oxymetazoline (14) • Vehicle (16)	Knee function composite, straight-leg raise, and successful pain management	The tested combination was well tolerated and resulted in reduced postoperative pain and improved knee function
Indication 5: Orthodontic pain					
Eslamian *et al.*, 2016, Iran[37]	Randomized, double-blind, crossover trial	20 Out-patients with orthodontic pain (35%, range 15-25 y)	• Placebo (20) • Benzocaine gel (20) • Ketoprofen gel (20)	Pain through a visual analogue scale ruler	Ketoprofen demonstrated a significant pain reduction compared to the placebo gel, with benzocaine having an effect mid-way between the two
Indication 6: Total hip arthroplasty					
Hirasawa *et al.*, 2018, Japan[39]	Double-blind, randomized, controlled trial	80 In-patients receiving total hip arthroplasty (15%, mean 63 y ± 10.5)	• Placebo (40) • Periarticular analgesic injection (PAI; 40)	Pain at rest 24 hours after surgery	Given the expense and lack of effectiveness, the authors do not recommend the use of this PAI in total hip arthroplasty; other mixtures or concentrations may be helpful in short-term admissions, but more research is needed

Abbreviations: "–", not mentioned; ACL, anterior cruciate ligament; BOP, bleeding on probing; ED, emergency department; PAI, periarticular analgesic injection; SRP, scaling and rootplaning.

[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
ACL reconstruction[13]	–	–	Irrigation solution	Irrigant	Once

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Ankle sprain[29,41]	2 g	2.5%	Gel	Topical	Once
Periodontitis[38,42]	Apply once weekly	1-2%	Gel, Poxoamen gel	Intracrevicular	4 weeks
Acute soft-tissue injury[40]	Apply 12-15 g/day	2.5%	Gel	Topical	5 days
Orthodontic pain[37]	Apply twice daily	0.16%	Gel	Topical	3 days
Total hip arthroplasty[39]	20 mL per injection	0.0833%	Solution	Periarticular injection	3 injections

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Ketoprofen 0.687 g/L / Amitriptyline HCl 0.227 g/L / Oxymetazoline HCl 0.215 g/L – sterile solution for injection[13]	1
	Ketoprofen 2.29 mg/mL / Nifedipine 1.04 mg/mL – sterile solution for injection	0

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Orthodontic pain[37]	• Manufactured in the Pharmacy School of Shahid Beheshti University of Medical Sciences • Carbomer 934P (50 g) as the gelling agent • Methylparaben (5 g) and propylparaben (1 g) as preservatives • Glycerine (400 mL) as humectant • Sodium hydroxide as pH adjusting agent • Ketoprofen 250 g • Enough ethanol as the co-solvent, and distilled water to reach the desired concentration	Gel	1.60 mg/mL
Periodontitis[38]	• 200 mL distilled water was added to 4 g sodium carboxymethyl cellulose, shaking and leaving to rest to produce an opalescent gel • Citric acid and sodium bicarbonate were dissolved in the minimum amount of water with either 2 g (1%) or 4 g (2%) ketoprofen. • Dissolved solution was added to gel under gentle heat and shaking.	Gel	1-2%

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. Fourteen SMEs discussed ketoprofen. Amongst these 14 SMEs, there were 5 medical doctors, 4 physician assistants, and 5 dentists. The SMEs specialized and/or were board-certified in anesthesiology, dentistry, internal medicine, orthopedics, pain management, rheumatology, sexual/reproductive health, and urology, working in academic medical center, hospital/health system, private practice/clinic, and retired. The SMEs had been in practice for 5 to 25 years.

In dentistry, one SME said that they like to use oral NSAIDs in their practice as opposed to other pain medications due to their antipyretic and anti-inflammatory properties. In addition, they would be less worried about NSAIDs leading to increased stomach ulceration due to the short period of time the patient would be on the drug (7-10 days), so long as the patient did not have any history of pre-existing conditions (such as gastrointestinal bleed) and were not on another NSAID or something else that would interact. In addition, they used oral ketoprofen a fair amount in their patient population because while their patients had never heard of ketoprofen, they had heard of ketamine and assumed that it was a similar drug. As a result, they were more likely to give it a chance to work, as compared to OTC NSAIDs such as ibuprofen, and the SME did not have to prescribe narcotics. Another SME said that they used oral ketoprofen occasionally, as an alternative NSAID; it lasts longer, is more potent than ibuprofen, and some people seem to like it. However, they have not used it recently. Other dental SMEs said they had never heard of it and never used it; "I would be really surprised if any dentists that I know were using that." As far as topical ketoprofen is concerned, several SMEs said that it would depend on if the base was safe for application inside the mouth. Another SME said that they might want to use a topical gel if it is able to target the source of pain at the site – but they typically use topical formulations of local anesthetics such as Orajel® (benzocaine). Orajel® is used for pain relief with toothaches or ulcers, but they "think it works more effectively for mucosal pain than tooth pain but for the most part, that's all [they] can really think of, in terms of a topical formulation that would be often applied in dentistry."

In urology, one SME said that they do not use the ketoprofen / nifedipine combination in their practice. Another said that it is "not something [they] use on a regular basis either. [They] think maybe this is used for stents, but [they] can't really comment that much on it."

None of the SMEs had used the amitriptyline / ketoprofen / oxymetazoline combination product in their practice. The SMEs who worked in rheumatology could see it working for inflammatory conditions as an intramuscular injection, but not as an agent for irrigation or instillation or as an intraarticular injection. One SME saw a potential for ketoprofen as a topical formulation for joint pain with amitriptyline and oxymetazoline.

Another SME said that they first started using compounded ketoprofen and cyclobenzaprine cream for patients with musculoskeletal injuries in pilots; this patient population was prohibited to take anything orally while flying, so topical pain creams allowed their strain or sprain to be treated and for the patient to keep working without worrying about side effects. They also reported using topical pain creams for tendonitis in the hand and elbow, and for knee and hip arthritis, mostly ketoprofen with cyclobenzaprine, sometimes with gabapentin added for numbness, tingling, or other nerve issues. Another SME said that while they have seen ketoprofen in some topical formulations, they use topical diclofenac because that is the one that the pharmacy recommends.

Several SMEs said that they had used compounded topical creams in the past but stopped due to issues with the pharmacies that provided the products. One SME said that patients received refills they had not

requested, so they have stopped using compounded products and currently use PENNSAID® (diclofenac topical solution) and ketoprofen. The SME said that they miss the compounded products based on patient feedback and response but have patients who say that cannabidiol (CBD) cream works well.

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.

Among respondents, 1 (100%) used ketoprofen. The respondent used ketoprofen as a topical gel (1, 100% of respondents) for both inflammatory pain and other: temporomandibular joint (TMJ) pain (refer to Table 12).

The survey respondent utilized compounded ketoprofen due to a lack of commercial products available in the dosage form, strength, or combination needed (1, 100%), explaining "We often combine it with cyclobenzaprine." Refer to Table 13 for reasons for using compounded ketoprofen.

The respondent (1, 100%) did not stock non-patient-specific compounded ketoprofen at their practice. The respondents did not answer the question about where compounded ketoprofen was obtained. Refer to Table 14.

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. One respondent (0.34% of 290 responses, where respondents were allowed to select multiple drug products) obtained combination amitriptyline / ketoprofen / oxymetazoline from a 503B outsourcing facility, while 3 respondents (1.03% of 290 responses, where respondents were allowed to select multiple drug products) obtained combination ketoprofen / nifedipine from a 503B outsourcing facility (refer to Table 15).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 16).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, 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)	1
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	0
Physician Assistant (PA)	0
Practice Setting	**Responses, n (N=1)**
Physician office or private practice	0
Outpatient clinic	0
Hospital or health system	0
Academic medical center	1
Emergency room	0
Operating room	0

Table 12. Conditions for which ketoprofen prescribed or administered

Condition	Responses, n (N=2)[a,b]
Urological procedures	0
Arthroscopic surgery	0
Inflammatory pain	1
Dental pain	0
Other: temporomandibular joint (TMJ) pain	1
No Response	0

[a]Out of 1 respondent, 1 reported prescribing or using ketoprofen.
[b]Survey respondents allowed to select multiple products.

Table 13. Reasons for using compounded ketoprofen

Reason	Responses, n (N=1)[a]
Commercial product not available in desired dosage form, strength, or combination	1
Patient allergies prevent use of commercial products	0
Patient conditions prevent use of commercial products	0
No commercial products	0

[a]Out of 1 respondent, 1 reported prescribing or using ketoprofen.

Table 14. Use of non-patient-specific compounded ketoprofen

Do you stock non-patient-specific compounded ketoprofen at your practice?	**Responses, n (N=1)**
Yes	0
No	1
Not sure	0
No response	0
How do you obtain your stock of non-patient-specific compounded ketoprofen?	**Responses, n (N=1)**
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	0
No response	1

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	**Responses, n (N=230)**
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	**Responses, n (N=290)[a]**
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3

Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanil	4
Sufentanil	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

[a]Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=686)[a,b]
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other[b]	40

[a]Survey respondents were allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Ketoprofen was nominated for inclusion on the 503B Bulks List as a topical gel, irrigation solution, and musculoskeletal injection to treat acute and chronic inflammatory conditions, dental pain, and for urological and arthroscopic surgery procedures. Ketoprofen is available in the nominated dosage form and ROA in Abu Dhabi, Belgium, Ireland, Latvia, Namibia, Saudi Arabia, and the UK.

From the literature review and interviews, topical NSAIDs have benefits over oral NSAIDs for osteoarthritis as far as providing symptom relief with a low incidence of side effects. However, ketoprofen gels were briefly withdrawn from the French market due to risk of severe cutaneous disorders being greater with ketoprofen when compared to other topical NSAID-based gels. Indications for topical ketoprofen included acute soft-tissue injury, ankle sprain, periodontitis, and orthodontic pain. In addition, ketoprofen was used as an irrigation solution with amitriptyline and oxymetazoline for ACL reconstruction and as a periarticular injection for total hip arthroplasty. Amongst SMEs in dentistry, one reported using oral ketoprofen regularly in their practice, one used it occasionally, and others had never heard of it or used it. The SMEs would consider topical ketoprofen so long as it was safe for application in the mouth, but currently they use topical local anesthetics. Practitioners in urology were unfamiliar with the use of combination ketoprofen and nifedipine; practitioners in rheumatology said the same for ketoprofen in the nominated ROA but saw potential for topical ketoprofen with amitriptyline and oxymetazoline. Several practitioners in orthopedics, pain management, and rheumatology had previously utilized ketoprofen as a component in topical pain creams, but issues with the compounding pharmacy made them switch to alternative forms of therapy.

One person responded to the survey distributed via professional medical associations and available on the project website. The indications listed were inflammatory and TMJ pain. The reason for using compounded ketoprofen over an FDA-approved product was that a commercial product was not available in the desired dosage form, strength, or combination, with the clarification, “We often combine it with cyclobenzaprine.” The respondent did not stock compounded ketoprofen at their practice. Two hundred thirty people responded to the survey distributed via the ASCA. One respondent obtained combination amitriptyline / ketoprofen / oxymetazoline, while 3 respondents obtained combination ketoprofen / nifedipine from a 503B outsourcing facility (where respondents were allowed to select multiple drug products).

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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 March 4, 2020
- Date last searched: March 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 401

1	ketoprofen/	2729
2	keprofen$.tw.	0
3	ketoprofen$.tw.	3814
4	ketoprophen$.tw.	13
5	or/1-4	4272
6	administration, topical/	38040
7	administration, buccal/	960
8	administration, mucosal/	249
9	infusions, parenteral/	26196
10	injections/	42190
11	injections, intramuscular/	30790
12	administration, intravesical/	3927
13	instillation, drug/	1439
14	therapeutic irrigation/	17365
15	buccal$.tw.	26792
16	gels/	28565
17	topical$.tw.	102607
18	mucosal$.tw.	117593
19	intramuscular$.tw.	51469
20	intra muscular$.tw.	706

21	inject$.tw.	727422
22	infusion$.tw.	241612
23	instill$.tw.	27074
24	irrigat$.tw.	32454
25	intravesical$.tw.	9535
26	intra vesical$.tw.	120
27	gel?.tw.	303246
28	or/6-27	1601875
29	exp pain/	388906
30	pain management/	32804
31	analgesia/	19720
32	ad.fs.	1393425
33	de.fs.	2949324
34	dt.fs.	2184138
35	tu.fs.	2191215
36	su.fs.	1958923
37	exp urologic diseases/	742930
38	exp dental diseases/	518553
39	exp orthodontics/	51769
40	pain$.tw.	672598
41	analgesi$.tw.	120312
42	((bladder or kidney or renal or ureter$ or urethra$ or urin$) adj3 (calcul$ or stone?)).tw.	28494
43	cystolith$.tw.	502
44	renolith$.tw.	4
45	nephrolith$.tw.	9488
46	ureterolith$.tw.	1119

47	urolith$.tw.	7902
48	dental$.tw.	213822
49	dentist$.tw.	69783
50	tooth?.tw.	84587
51	teeth?.tw.	106452
52	orthodont$.tw.	37870
53	periodont$.tw.	73869
54	or/29-53	8848582
55	and/5,28,54	780
56	exp animals/ not humans/	4675019
57	55 not 56	475
58	limit 57 to english language	401

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 438

1	ketoprofen'/mj	4362
2	keprofen*':ti,ab,tn	0
3	ketoprofen*':ti,ab,tn	5381
4	ketoprophen*':ti,ab,tn	33
5	#1 OR #2 OR #3 OR #4	6786
6	buccal drug administration'/de	655
7	injection'/exp	247457
8	intramuscular drug administration'/de	71562
9	drug instillation'/de	1782
10	intravesical drug administration'/de	2638
11	periodontal drug administration'/exp	20
12	bladder irrigation'/de	2298
13	topical drug administration'/de	81519
14	mucosal drug administration'/de	417
15	buccal*':ti,ab	34453
16	topical*':ti,ab	146042
17	mucosal*':ti,ab	167763
18	inject*':ti,ab	1081834
19	infusion*':ti,ab	352414
20	instill*':ti,ab	40130
21	irrigat*':ti,ab	44098
22	intravesical*':ti,ab	14410

23	intra vesical*':ti,ab	278
24	intramuscular*':ti,ab	74330
25	intra muscular*':ti,ab	1269
26	gel'/de	32912
27	gel$':ti,ab	357513
28	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	2274408
29	pain'/exp	1359568
30	analgesia'/de	125929
31	postoperative analgesia'/de	16773
32	urinary tract disease'/exp	1491068
33	tooth disease'/exp	241604
34	orthodontics'/de	35903
35	drug therapy':lnk	3842481
36	therapy':lnk	4918817
37	drug dose':lnk	621758
38	surgery':lnk	2139835
39	pain*':ti,ab	1035177
40	analgesi*':ti,ab	177645
41	((bladder OR kidney OR renal OR ureter* OR urethra* OR urin*) NEAR/3 (calcul* OR stone*)):ti,ab	45384
42	cystolith*':ti,ab	895
43	renolith*':ti,ab	8
44	nephrolith*':ti,ab	16135
45	ureterolith*':ti,ab	1809
46	urolith*':ti,ab	11758
47	dental*':ti,ab	234399
48	tooth$':ti,ab	91937

49	teeth$':ti,ab	114146
50	orthodont*':ti,ab	39616
51	periodont*':ti,ab	76614
52	dentist*':ti,ab	75490
53	#29 OR #30 OR #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 OR #48 OR #49 OR #50 OR #51 OR #52	8836232
54	#5 AND #28 AND #53	813
55	[animals]/lim NOT [humans]/lim	6000726
56	#54 NOT #55	570
57	#54 NOT #55 AND [english]/lim	438

Appendix 2.1. Survey instrument for professional medical associations (single agent)

Welcome. We want to understand your clinical use of compounded ketoprofen. 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 ketoprofen to your patients?

   - o Yes
   - o No

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

   - o Intramuscular injection
   - o Irrigation solution
   - o Topical gel
   - o None of the above

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

   - o Arthroscopic surgery
   - o Dental pain
   - o Inflammatory pain
   - o Urological procedures
   - o Other (please explain) _____

5. I use compounded ketoprofen 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 ketoprofen.
    - o Other (please explain) _____

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

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

7. I obtain compounded ketoprofen 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 2.2. Survey instrument for professional medical associations (ketoprofen / nifedipine)

Welcome. We want to understand your clinical use of compounded ketoprofen / nifedipine as a combination product. 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 ketoprofen / nifedipine as a combination product to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer ketoprofen / nifedipine as a combination product by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Solution for injection
   - o None of the above

4. I prescribe or administer ketoprofen / nifedipine as a combination product for the following conditions or diseases: (check all that apply)

   - o Urological procedures
   - o Other (please explain) _____

5. I use compounded ketoprofen / nifedipine as a combination product 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 ketoprofen / nifedipine.
   - o Other (please explain) _____

6. Do you stock non-patient-specific compounded ketoprofen / nifedipine as a combination product at your practice?

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

7. I obtain compounded ketoprofen /nifedipine as a combination product 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 2.3. Survey instrument for professional medical associations (amitriptyline / ketoprofen / oxymetazoline)

Welcome. We want to understand your clinical use of compounded amitriptyline / ketoprofen / oxymetazoline as a combination product. 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 amitriptyline / ketoprofen / oxymetazoline as a combination product to your patients?

   - o Yes
   - o No

3. I prescribe or administer amitriptyline / ketoprofen / oxymetazoline as a combination product for the following conditions or diseases: (check all that apply)

   - o Irrigation in arthroscopic surgery
   - o Acute/chronic inflammatory conditions
   - o Other (please describe) _____

4. I use compounded amitriptyline / ketoprofen / oxymetazoline as a combination product 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 amitriptyline / ketoprofen / oxymetazoline
   - o Other (please explain) _____

5. Do you stock non-patient-specific compounded amitriptyline / ketoprofen / oxymetazoline as a combination product at your practice?

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

6. I obtain compounded amitriptyline / ketoprofen / oxymetazoline as a combination product 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) _____

7. 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) _____

8. 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 2.4. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk 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

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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 utilize a 503B outsourcing facility to acquire compounded drugs?

   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

   - o I do not obtain any compounded drugs from 503B outsourcing facilities
   - o Amitriptyline / Ketoprofen / Oxymetazoline
   - o Budesonide
   - o Calcium gluconate
   - o Droperidol
   - o Epinephrine
   - o Epinephrine for ophthalmic administration
   - o Epinephrine / Lidocaine for ophthalmic administration
   - o Epinephrine / Bupivacaine / Fentanyl
   - o Fentanyl
   - o Flurbiprofen
   - o Flurbiprofen for ophthalmic administration
   - o Hydromorphone
   - o Ipamorelin
   - o Ketoprofen / Nifedipine
   - o Lidocaine / Epinephrine / Tetracaine HCl
   - o Meperidine
   - o Morphine
   - o Naloxone
   - o Neomycin
   - o Phentolamine
   - o Promethazine

- o Remifentanil
- o Sufentanil
- o Tramadol
- o None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

    - o Dental
    - o Dermatology
    - o Endoscopy
    - o Neurosurgery
    - o Obstetrics/gynecology
    - o Ophthalmology
    - o Otolaryngology
    - o Orthopedics
    - o Pain
    - o Plastics
    - o Podiatry
    - 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.