Summary Report

Hydroxocobalamin Hydrochloride

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Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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REVIEW OF NOMINATION

Hydroxocobalamin hydrochloride (hydroxocobalamin HCl; UNII code: Q40X8H422O) was nominated for inclusion on the 503B Bulks List by Fagron for use in vitamin B12 deficiency as a 5mg/mL intravenous injection.

The reason provided for nomination to the 503B Bulks List is that there are no FDA approved products containing hydroxocobalamin HCl. While cyanocobalamin is currently FDA approved for vitamin B12 deficiency, studies have found that it is important to include hydroxocobalamin, especially in patients undergoing long-term hemodialysis where it has been shown to reduce erythropoietin requirement.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of hydroxocobalamin 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 hydroxocobalamin HCl; name variations of hydroxocobalamin 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 hydroxocobalamin 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 December 20, 2018. The search included a combination of ("Hydroxocobalamin"[TIAB] OR "vitamin b12a"[TIAB]) AND ("humans"[MeSH Terms] AND "English"[lang] NOT autism) AND ("clinical"[TIAB] OR "therapy"[TIAB] OR "treatment"[TIAB] OR "therapeutic"[TIAB] OR "deficiency"[TIAB]). Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to RefWorks®, merged, and sorted for removal of duplicate citations. Covidence® was used for screening purposes.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of hydroxocobalamin HCl or the implementation of hydroxocobalamin HCl in clinical practice. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

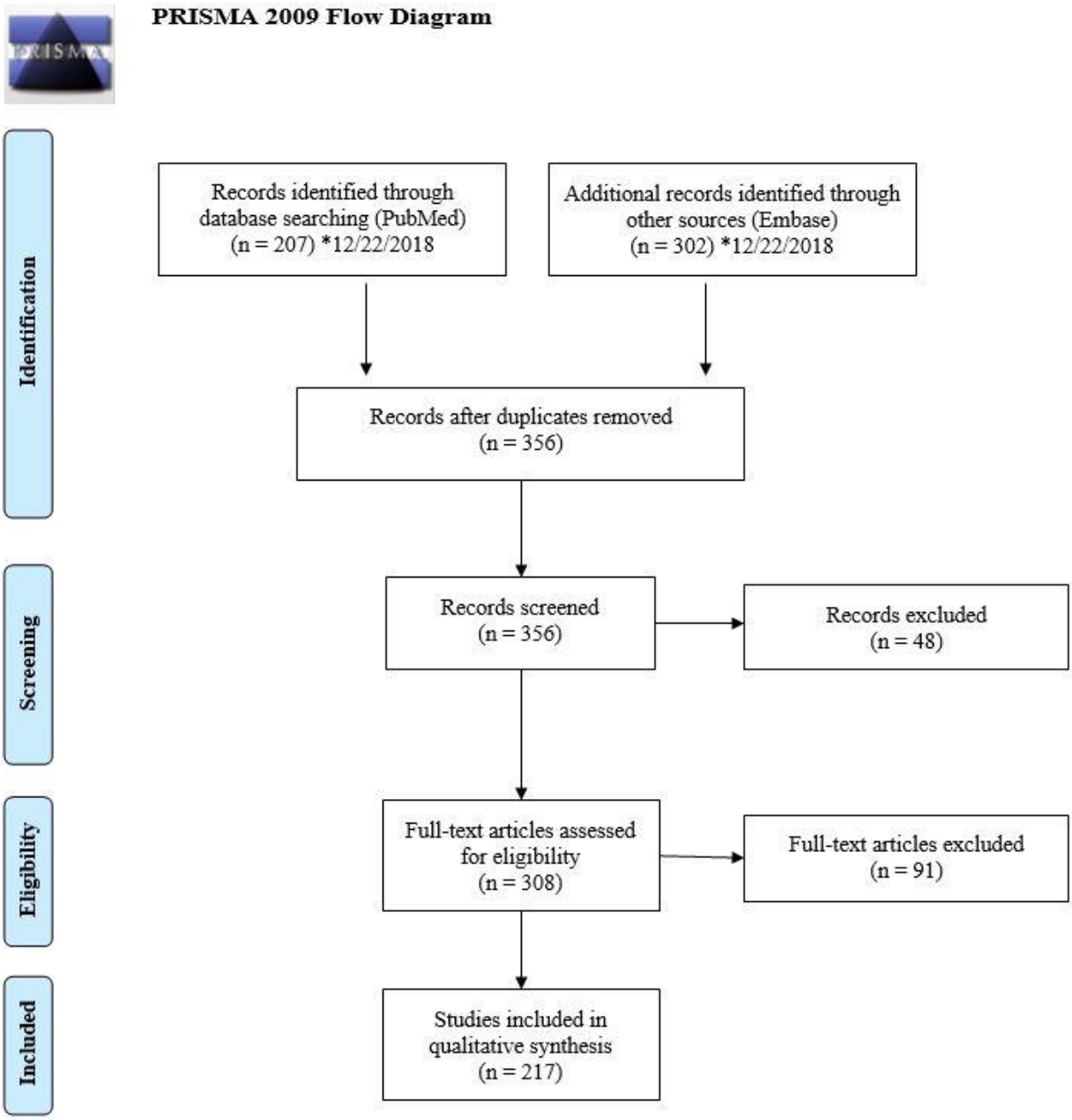
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for hydroxocobalamin 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 hydroxocobalamin 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). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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

Outreach to medical specialists and specialty organizations

Using the indication from the nomination and the results of the literature review, seven (7) medical specialties that would potentially use hydroxocobalamin HCl were identified: cardiology, hematology, naturopathy, neurology, ophthalmology, primary care, and toxicology. Semi-structured interviews were conducted with subject matter experts within this/these specialties. 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) experts were contacted for interviews, of which one (1) accepted. One (1) expert specializing in neurology failed to respond to the interview request. 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 cardiology, hematology, naturopathy, neurology, ophthalmology, primary care, and toxicology, identified from the nomination, 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 twelve (12) associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

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

Table 1. Participating associations

Specialty	Association
Naturopathy	American Association of Naturopathic Physicians (AANP)
Ophthalmology	American Society of Cataract and Refractive Surgery (ASCRS)
	American Society of Retina Specialist (ASRS)
Primary Care	American Academy of Environmental Medicine (AAEM)
Toxicology	American College of Medical Toxicology (ACMT)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Hematology	American Society of Hematology (ASM)	Failed to respond
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Ophthalmology	American Academy of Ophthalmology (AAO)	"I would take this off the list"
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Hydroxocobalamin HCl is available as an FDA-approved product and an OTC product in the US; and there is a current USP monograph.
- Hydroxocobalamin HCl is available in Abu Dhabi, Belgium, Canada, Hong Kong, Ireland, Latvia, and UK.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date
Hydroxocobalamin	1mg/mL, 5g/vial	Injectable	Injection	Prescription	Prior to 1/1/1982

Abbreviations: ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Hydroxocobalamin	5g/vial, 1mg/mL	Injection	–	Abu Dhabi	Active	–
	5g, 5mg/2mL	Powder, injection		Hong Kong	Prescription	8/13/1982
	1mg/ml	Solution		Ireland	Prescription, non-renewable	5/6/1995
	2.5-5g	Powder		Latvia	Prescription	11/23/2007
	5g/vial		Intravenous	Belgium		10/6/2010
				Canada		10/19/2012
				UK		11/23/2007

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

[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.

Summary of literature review

- Total number of studies included: 217 (172 descriptive, 27 experimental, and 18 observational).
- Most of the studies were from the US (74).
- The most common indication for use in the US and non-US studies were cyanide toxicity and cobalamin-related re-methylation disorder.
- Compounded products were identified from both the US and non-US studies.

Table 5. Types of studies

Types of Articles	Number of Studies
Descriptive[1-172]	172
Experimental[173-199]	27
Observational[200-217]	18

Table 6. Number of studies by country[a]

Country	Number of Studies
Australia[30,61,98,134,189,217]	6
Austria[14,133]	2
Belgium[6,54,56]	3
Brazil[7,185,186]	3
Canada[9,33,40,60,62,91,139,140,204,216]	10
China[42,89,111,113]	4
Denmark[197,210]	2
Finland[107,192]	2
France[3,16,17,25,67-71,81,83,93,119,129,159,176,177,200,201]	19
Germany[97,105,144,172]	4
Guam[125]	1
India[164]	1
Ireland[28]	1
Italy[8,21,39,44,55,65,110,116,117,122,142,162]	12

Japan[75]	1
Luxembourg[143,195]	2
Morocco[211]	1
The Netherlands[104,106,152,183,190,196,198,199,208]	9
New Zealand[13,26]	2
Nigeria[193,194]	2
Portugal[46,47]	2
Romania[45]	1
Saudi Arabia[124]	1
Serbia[155]	1
Spain[58,64,118,141]	4
Sweden[34,108,188]	3
Switzerland[32,74,101,145,191]	5
Taiwan[66,168,180]	3
Turkey[84,102,174]	3
UK[1,11,12,18,20,29,41,48,51,109,136,153,156-158,173,178,179,181,182,203,205,212,215]	24
US[2,4,5,10,19,22-24,31,35-38,43,50,52,53,57,59,63,72,73,77-80,82,85-88,90,92,96,99,100,103,112,114,115,120,121,123,126-128,130-132,135,137,138,146-151,160,161,163,165-167,170,171,175,184,187,202,206,209,213,214]	74
Multiple Countries • Belgium, France, Germany, Italy, Spain[76] • Italy, Spain, Sweden[49] • Malaysia, UK[169] • Spain, Columbia[154] • Switzerland, Austria, Italy, UK[94] • Switzerland, Austria[95] • Switzerland, Germany[207] • UK, Switzerland[27] • US, Canada[15]	9
Total US[b]: 75 Total non-US Countries[b]: 145	

[a]Studies 70, 88, and 135 did not mention the country.
[b]Studies 47, 90, 157, 177, 178, 200, and 201 counted in both US and non-US total.

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US[a]

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Cyanide toxicity[2,10,19,38,50,52,59,77,80,82,85-88,90,92,96,99,120,121,127,128,130,135,138,148,151,163,166,171,184,209,213,214]	0.5-15g	–	Solution	Intravenous	Once
Cobalamin-related re-methylation disorder[5,15,31,37,57,73,103,115,123,126,137,149,150,160,165,170,175,202]	0.4mg/month-20mg/day	1-2%	–	Intramuscular	Once-3.5 years
	37.5-262.5mg/week	–	–		At least 16 weeks
	1-2mg/1-2 days	–	–	Oral	1 month-5 years
Vasoplegic syndrome[4,24,35,36,43,112,131,146,147,167,206]	0.125-5g	–	–	Intravenous	Once or twice
	250-500mg/hour	–	–		Intraoperative
Vitamin B12 deficiency[53,78,161]	0.01-1mg	–	–	Intramuscular	Once
	1mg/6 weeks-0.5mg/day	–	–		10 days-12 weeks
Carbon monoxide exposure[22,135]	–	–	–	–	–
Bronchial squamous metaplasia[187]	0.5mg/day	0.5mg/capsule	Capsule	Oral	4 months
Chronic erythrocytic hypoplasia[79]	–	–	–	–	–
Hydrogen sulfide toxicity[114]	–	–	–	–	–
Leber's hereditary optic atrophy[72]	1-2mg/week	–	–	Intravenous	–

Refractory hypotension due to septic shock[23]	5g	–	Solution	Intravenous	Once
Severe combined immunodeficiency (SCID)[100]	–	–	–	Intramuscular	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]Study 135 had multiple indications.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Cobalamin-related remethylation disorders[9,15,17,20,27,33,34,39,42,51,55,61,81,83,84,89,94,95,98,101,102,105-107,110,111,113,118,122,124,129,133,139,141,143-145,152,157,159,162,169,172,179,190,195,207]	1.5-10.5mg/week	0.075%	Solution	Intranasal	4 weeks
	1mg/2 weeks-40mg/day	–	Solution	Intramuscular	15 weeks-30 months
	1mg/day	–	–	Intravenous	10 days
	1mg/day-25mg/week	–	–	Subcutaneous	–
	1mg/day-20mg/week	–	–	Oral	1 month
Cyanide toxicity[3,6,7,13,16,18,25,26,30,32,40,44-47,49,54,56,62,67-71,74,76,93,97,108,116,117,119,125,134,142,153,158,174,177,200,201,204,216]	1mg	–	–	Intramuscular	Once
	2.5g	–	–	Intraosseous	Once
	2.5-20g	–	Solution	Intravenous	1-4 times
	80-125mg/kg	–	–		Once
Vitamin B12 deficiency[1,11,12,28,29,155,156,168,173,176,181,189,191,196-198,208,210-212]	0.25mg/month-4mg/week	–	–	Intramuscular	Once-20 years
	15mg/month-15mg/day	–	–	Oral	–
Anemia, Vitamin B12 deficiency[41,140,178,183,188,203,215]	0.25-28mg/month	0.1%	–	Intramuscular	Once-3 months

Amblyopia[109,182,205]	1mg/month-5mg/day	–	–	Intramuscular	6 weeks-10 months
General poisoning[21,58,64]	–	–	–	–	–
Ataxic neuropathy[193,194]	1-5mg/1-2 weeks	–	Injection	–	36-48 weeks
Compressive neuralgia[185,186]	6mg/day	–	Capsule	Oral	30 days
Homocystinuria due to cystathionine β-synthase deficiency[65,217]	1mg/week	–	–	–	–
Hyperhomocysteinemia in end-stage renal disease[60,91]	1mg/week	–	–	Intravenous	4-8 weeks
	1mg/week	–	–	Subcutaneous	16 weeks
Nitrous oxide toxicity[48,66]	1mg/day	–	–	Intramuscular	–
Hereditary folate malabsorption[154]	–	–	–	–	–
Hydrogen sulfide toxicity[75]	2.5g	–	–	Intravenous	–
Leber's hereditary optic atrophy[192]	–	–	–	–	–
Migraine prophylaxis[199]	1mg/day	2%	Solution	Intranasal	–
Nocturnal leg cramps[180]	0.75mg/day	–	Capsule	Oral	6 weeks
Optic neuritis[164]	0.5-1mg/day	–	–	Intramuscular	–
Sodium azide toxicity[14]	–	–	–	–	Once
Subacute combine degeneration (SCD)[136]	1mg/week	–	–	Intramuscular	–
Transcianocobalamin C deficiency[8]	–	–	–	Intravenous	–
Vasoplegic syndrome[104]	–	–	–	Intravenous	–

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Cyanide toxicity[77,82,87,88,171]	1993-2016	• Hydroxocobalamin in dextrose solution	Solution	0.1%
		• Hydroxocobalamin reconstituted with normal saline	Solution	2.5%
Bronchial squamous metaplasia[187]	1988	• Hydroxocobalamin with folic acid	Capsule	0.5mg/capsule

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Cyanide toxicity[44,68,93]	• Hydroxocobalamin in saline solution or water	Solution	2.5-5%

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

One (1) interview was conducted.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Hydroxocobalamin HCl	Interview Summary Response
OPH_05	MD	Ophthalmology	Academic medical institution	No	• If a patient has optic neuritis due to B12 deficiency, would give the diagnosis, but would not administer vitamin B12. Refer patient to the primary physician. • Stated that it is an old practice and nobody is doing it.

Abbreviation: MD, Doctor of Medicine.

Summary of survey results

Table 13. Characteristics of survey respondents [75 people responded to the survey[a]]

Board Certification	DO	MD	ND	PharmD	PhD	No Response
Addiction Medicine	0	3	0	0	0	0
Clinical Pharmacology	0	1	0	0	0	0
Emergency Medicine	5	25	0	0	0	0
Family Medicine	0	1	0	0	0	0
Internal Medicine	0	5	0	0	0	0
Medical Toxicology	3	31	0	0	1	0
National Registry of Certified Chemists	0	0	0	0	1	0
Naturopathic Doctor	0	0	5	0	0	0
Naturopathic Physician	0	0	4	0	0	0
Nephrology	0	1	0	0	0	0
Occupational Medicine	0	2	0	0	1	0
Ophthalmology	0	4	0	0	0	0
Pediatrics	0	2	0	0	0	0
Preventive Medicine	0	1	0	0	0	0
Toxicology	0	0	0	1	0	0
No Response	0	0	0	0	0	26

Abbreviations: DO, Doctor of Osteopathic Medicine; MD, Doctor of Medicine; ND, Naturopathic Doctor; PharmD, Doctor of Pharmacy; PhD, Doctor of Philosophy.

[a]Some respondents reported more than one (1) terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=54[a])
Compounded	2
FDA-approved	34
Over-the-counter	0
Dietary	1
Unsure	2
No Response	16

[a]Out of 75 respondents, 54 reported using, prescribing, or recommending multiple types of hydroxocobalamin HCl product.
[c]Some respondents reported using more than one (1) type of product.

Table 15. Compounded use of hydroxocobalamin HCl in practice[a]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Cyanide poisoning	1-4g	Once	Solution	Intravenous	Once	–

Abbreviations: "–", not mentioned; ROA, route of administration.
[a]One (1) respondent.

Table 16. Indications for which hydroxocobalamin HCl is considered a standard therapy[a]

Indication	Standard Therapy			
	Compounded, n (N=2)	**Non-compounded, n (N=34)**	**Unsure, n (N=2)**	**No Response, n (N= 16)**
Anemia	0	1	0	0
B12 deficiency	0	2	0	0
"Carbon monoxide"	0	1	0	0
Cardiac bypass procedure	0	2	0	0
Cyanide poisoning, including smoke inhalation	1	31	2	0
Thiocyanate toxicity	0	1	0	0
Vasoplegia	0	2	0	0
No Response	1	1	0	16

[a]Some respondents reported more than one indication.

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

Reasons
"Availability"

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

	Respondents, n (N=2)
No–use has remained consistent	0
Yes–I use it LESS often now	0
Yes–I use it MORE often now[a]	1
No Response	1

[a]One (1) respondent wrote "Better availability".

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

	Respondents, n (N=2)
No	1
Yes	0
No Response	1

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

No survey respondents provided this information

CONCLUSION

Hydroxocobalamin HCl (UNII code: Q40X8H422O) was nominated for inclusion on the 503B Bulks List for treatment of vitamin B-12 deficiency via a 5mg/mL intravenous injection. Hydroxocobalamin HCl is approved in Abu Dhabi, Belgium, Canada, Hong Kong, Ireland, Latvia, UK, and US.

From the literature review conducted, the most common indications for the use of hydroxocobalamin HCl in the US and non-US studies were cyanide toxicity and cobalamin-related re-methylation disorder. Compounded products were identified from both the US and non-US studies, however not for the nominated indication.

One (1) interviewee stated that using hydroxocobalamin HCl for vitamin B12 deficiency is an old practice that no one is currently doing. The interviewee would not use hydroxocobalamin HCl in the office because, as an ophthalmologist, they give the diagnosis and refer the patient to the primary physician for treatment of B12 deficiency.

From the survey responses, 54 out of 75 respondents used hydroxocobalamin HCl. The most common indication for use of compounded hydroxocobalamin HCl was cyanide poisoning. Availability was the reason for using the compounded hydroxocobalamin HCl product over an FDA-approved product. Zero (0) out of two (2) respondents who used compounded hydroxocobalamin HCl reported stocking compounded hydroxocobalamin HCl in the office.

APPENDICES

Appendix 1. References

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Appendix 2. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **hydroxocobalamin 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. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Hydroxocobalamin HCl

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

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

Display This Question:

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

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

_____

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

_____

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

_____

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

_____

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Hydroxocobalamin 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