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Taurine: Summary Report

Item Type	Report
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Publication Date	2020-02
Keywords	Taurine; Compounding; Food, Drug, and Cosmetic Act, Section 503B; Food and Drug Administration; Outsourcing facility; Drug compounding; Legislation, Drug; United States Food and Drug Administration
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Summary Report

Taurine

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:

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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.

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REVIEW OF NOMINATIONS

Taurine (UNII code: 1EQV5MLY3D) was nominated for inclusion on the 503B Bulks List by McGuff Compounding Services, Inc. (McGuff CPS), the Alliance for Natural Health USA (ANH-USA), the Integrative Medicine Consortium (IMC), and the American Association of Naturopathic Physicians (AANP) for use in cardiovascular disease, retinal degeneration, hepatic injury due to toxins, and growth and development. Taurine will be compounded as a 50mg/mL and 100mg/mL multi-dose and preservative-free intravenous and intramuscular injection.

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

- There are no FDA-approved products that contain taurine.
- FDA-approved drugs are more potent chemicals with more severe side effects. Thousands of patients with the disorders listed above are prescribed taurine by alternative and naturopathic physicians as a single or combination preparation for daily use.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of taurine 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 taurine; name variations of taurine 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 taurine. 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 (taurine[TIAB]) AND (retina[TIAB] OR growth[TIAB] OR development[TIAB] OR cardiovascular[TIAB] or heart[TIAB] or eye[TIAB] or degenerat*[TIAB]) AND (therapy[TIAB] OR therapeutic[TIAB] OR clinical[TIAB] OR treatment[TIAB]) AND English[lang] AND humans[MeSH] 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. Articles were considered relevant based on the identification of a clinical use of taurine or the implementation of taurine 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 taurine 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 taurine 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

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, nine (9) medical specialties that would potentially use taurine were identified: cardiology, endocrinology, hepatology, naturopathy, neurology, oncology, ophthalmology, pediatrics, and primary care. Semi-structured interviews were conducted with subject matter experts within 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. Five (5) experts were contacted for interviews, of which one (1) accepted. Two (2) of the experts who were contacted, one (1) specializing in hepatology and one (1) specializing in ophthalmology, replied with a statement that they do not utilize the substance. Two (2) experts, one (1) specializing in neurology and one (1) in oncology, failed to respond to the interview request. The interview was 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, endocrinology, hepatology, naturopathy, neurology, oncology, ophthalmology, pediatrics, and primary care, identified from the nominations, literature review, and interviews, 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 14 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)			
On h th a long la gru	American Society of Cataract and Refractive Surgery (ASCRS)			
Ophthalmology	American Society of Retina Specialist (ASRS)			
Pediatrics	American Academy of Pediatrics (AAP)			
Primary Care	American Academy of Environmental Medicine (AAEM)			

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Endocrinology	American Association of Clinical Endocrinologists (AACE)	Declined, "endocrinologists are not generally in the compounding space."
Hepatology	American Association for the Study of Liver Diseases (AASLD)	Failed to respond
Madicina	American Medical Association (AMA)	Failed to respond
Wedicille	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond
Oncology	American Society of Clinical Oncology (ASCO)	Declined, "they are unable to share survey with members"
Ophthalmology	American Academy of Ophthalmology (AAO)	Declined, "I believe this is experimental and should be used under an IRB if people are giving periocular or intra ocular injections of it. Challenge the nominator to name anyone using it clinically. I would drop it from 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

- Taurine is not available as an FDA-approved product.
- Taurine is available as oral OTC natural supplements in the US.
- There is a current United States Pharmacopeia (USP) monograph for taurine.
- Taurine is not available as a single ingredient product in any of the national medical registries searched. However, taurine is available as part of multiple ingredient intravenous products in Abu Dhabi, Australia, Belgium, Canada, the EU, Hong Kong, Ireland, Latvia, New Zealand, and the UK.

Table 3. Currently approved products - US

No approved products in the US

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

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

Summary of literature review

- Total number of studies included: 63 (34 descriptive, 26 experimental, and 3 observational).
- Most of the studies were from the US (18).
- The most common indications for the use of taurine in both the US and non-US studies were heart failure and diabetes.
- Compounded products were identified from the non-US studies, but not as the nominated intravenous or intramuscular injection.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive ¹⁻³⁴	34
Experimental ³⁵⁻⁶⁰	26
Observational ⁶¹⁻⁶³	3

Table 6. Number of studies by country

Country	Number of Studies
Argentina ⁵⁰	1
Australia ^{34,53}	2
Brazil ⁴⁶	1
Canada ^{16,33,35,45,62,63}	6
China ⁵⁸	1
Denmark ⁴⁴	1
France ¹²	1
Germa ny ^{48,60}	2
Hungary ²²	1
Iran ⁴³	1
Ireland ^{26,51,59}	3
Italy ^{4,5,9-11,28,42,52,55}	10
Japan ^{1,13,15,21,37-41,56,57,61}	12
Russia ³⁶	1
Spain ⁸	1
Switzerland ²	1
US ^{3,6,7,17-20,23-25,27,29-32,47,49,54}	18
Multiple Countries	1
• China, Pakistan ¹⁴	1
	TotalUS: 18 TotalNon-US Countries: 45

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment	
Congestive heart failure ^{3,6,17,19,25,29,31}	3-6g/day	_	_	Oral	4-6 weeks	
Diabetes ^{18,25,27,29}	1-4g/day	_	_	_	30 days-8 weeks	
En:10003.25.49	200mg/kg	—	_	Intravenous	10US —	
Lphepsy	375-8000mg/day	_	Liquid	Oral	4-6 months	
Retinal dysfunction ^{6,7,29} , retinitis pigmentosa ³	1-2g/day	_	_	_	1 year	
Neurodegenerative diseases ^{25,29,32}	1.5-4g/day	_	_	_	_	
Adjunctive vigabatrin treatment ^{29,54}	50-200mg/kg/day	_	_	_	Up to 1 year	
Bile acid conjugation in infants ^{6,7}	45µM/kg/day	_	_	_	_	
Dyslipidemia ^{3,18}	3-6g/day	_	_	_	3-7 weeks	
Hypertension ^{20,29}	1.6-6g/day	_	_	_	6-12 weeks	
Ischemia reperfusion injury ^{29,30}	5g	_	Liquid	Intravenous	Once before surgery	
Steatorrhea in cystic fibrosis patients ^{3,25}	30mg/kg/day	_	_	_	4 months	
Acute hepatitis ³	12g/day	_	_	_	At least 1 week	
Alcohol withdra wal ³	3g/day	_	_	_	7 days	
Atherosclerosis ²⁹	_	_	_	-	_	
Atrial fibrillation due to Lyme disease ²⁴	525mg/day	_	_	_	_	
Bypass surgery supplement ¹⁷	3g/day	1.2%	Liquid	Oral	30-45 days	

Cancer ²³	525mg/day	_	_	_	_
Cognitive performance ⁴⁷	2000mg	_	Capsule	Oral	2 sessions
Cytoprotection ²⁷	_	_	_	_	_
Fragile X syndrome ²⁹	_	_	_	_	_
Mitochondrial disease ²⁹	_	_	_	_	_
Muscular dystrophy ²⁹	_	_	_	_	_
Myocardial arrhythmias ²⁹	_	_	_	Oral	_
Parenteral nutrition ⁷	_	_	_	_	_
Platelet aggregation ²⁵	1.5-4g/day	_	_	_	_
Rheumatoid arthritis ²⁹	_	_	_	_	_
Sarcopenia ²⁹	_	_	_	_	_
Stroke ²⁹	_	_	_	_	_

Abbreviations: "-", not mentioned; ROA, route of a dministration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment	
Heart failure ^{1,15,33-35,37-41,43,57,61}	1.5-6g/day	—	Capsule, Powder, Sachet	Oral	2 weeks-1 year	
Diabetes ^{8,10,11,13,14,33,59}	1-3g/day	_	_	Oral	30 days-4 months	
A diversitive vice hot in the star out 12,56,62,63	0.2-1.5g/day	_	Dovudor	_		
Adjunctive vigabatiin treatment	50-200mg/kg/day	_	Powder	_	At least 2 years	
CABG or valve replacement supplement ^{16,35,36}	500mg/day	_	_	Oral	30 days-12 weeks	
Hypertension ^{13,33,58}	1.5-6g/day	_	_	_	5 days-2 months	
Insulin secretion ^{13,14,44}	1.5-3g/day	_	Capsule	Oral	2-8 weeks	
Cardiac failure ^{2,26}	3g/day	_	_	Oral	6 weeks	
Cardiovascular risk ^{5,34}	3g/day	_	_	_	4 weeks	
Dry eye disea se ^{28,52}	Instill 3x/day	0.49%	Drops	Ophthalmic	15 days	
Glaucoma ^{42,55}	Instill4x/day	0.5%	Solution	Ophthalmic	90 days	
Ischemia reperfusion injury ^{26,50}	5g	_	Liquid	Intravenous	Once	
Obesity ^{13,21}	3-6g/day	_	_	_	3-7 weeks	
Atherosclerosis ³³	6g/day	_	_	_	_	
Cancer ²²	150-175mg	_	_	_	_	
Endothelial dysfunction in diabetes ⁵¹	1500mg/day	_	Tablet	Oral	14 days	

Humoral defense ²⁶	_	_	_	_	_
Litholysis ⁴⁸	2g/day	_	_	Oral	18 months
Oxidative stress ⁴⁶	3g/day	_	Capsule	Oral	8 weeks
Pars plana vitrectomy ⁶⁰	_	3mmol/L	Irrigation solution	Topical	During procedure
Postoperative cellular homeostasis ²⁶	_	_	_	_	_
Psychosis ⁵³	4g/day	_	_	_	12 weeks
Sepsis ²⁶	_	_	_	_	_
Skeletalmuscle disorders9	_	_	_	_	_
Steatorrhea in cystic fibrosis ⁴⁵	30mg/kg/day	_	Capsules	Oral	6 months
Vitiligo ⁴	_	_	Gel capsules	Oral	_

Abbreviations: "-", not mentioned; ROA, route of a dministration.

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Oxidative stress ⁴⁶	• "Ta urine and placebo capsules were manipulated by the Department of Industrial Pharmacy of the School of Medicine of Ribeirão Preto, University of São Paulo"	Capsule	_

Abbreviation: "-", not mentioned.

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 Taurine	Interview Summary Response
END_02	MD	Endocrinology, Diabetes, and Metabolism	Academic medical institution	No	• Does not use or know of any literature that states it would be helpful.

Abbreviation: MD, Doctor of Medicine.

Summary of survey results

Board Certification	MD	ND	PharmD	No Response
Anesthesiology	7	0	0	0
ClinicalPharmacology	1	0	0	0
Critical Care Medicine	3	0	0	0
Fellow of the American Board of Naturopathic Oncology	0	1	0	0
Gastroenterology	1	0	0	0
Hospice & Palliative Medicine	1	0	0	0
Naturopathic Doctor	0	6	0	0
Naturopathic Physician	0	5	0	0
Ophthalmology	4	0	0	0
Pediatric Anesthesiology	3	0	0	0
Pediatrics	5	0	0	0
No Board Certification	1	2	1	0
No Response	0	0	0	16

Table 13. Characteristics of survey respondents [40 people responded to the survey^a]

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor; PharmD, Doctor of Pharmacy. ^aSome 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=8ª)		
Compounded	1 ^b		
FDA-approved	1		
Over-the-counter	2		
Dietary	5		
Unsure	0		
No Response	2		

^aOut of 40 respondents, eight (8) reported using, prescribing, or recommending multiple types of taurine product. ^bOne (1) respondent used in combination: "meyers."

Table 15. Compounded use of taurine in practice

No survey respondents provided this information

	Standard Therapy				
Indication	Compounded, n (N=1)	Non-compounded, n (N=5)	No Response, n (N=2)		
Blood sugar management	0	1	0		
Cardiac arrhythmias	0	1	0		
Cystic fibrosis	0	1	0		
Dia betic retinopathy	0	1	0		
Heart failure	0	1	0		
Heart problems	0	1	0		
Macular degeneration	0	1	0		
Other ^b	0	1	0		
Psychotropic medication discontinuation	0	1	0		
Seizure disorders	0	1	0		
No Response	1	0	2		

Table 16. Indications for which taurine is considered a standard therapy^a

^aSome respondents reported more than one indication. ^b"Varies depending on individual patient circumstances."

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Table 17.	Reasons	TOP USING	compounded	DFOOLUCE INSIEMO	ог ше гра-ар	Droved broducis
10010 1/1	1.0000000	- or #01118	• omp o ana • a	product motore	or and i bit ap	proved produced

	Reasons
"Quality"	

	Respondents, n (N=1)
No-use has remained consistent	0
Yes–I use it LESS often now	1
Yes–I use it MORE often now	0

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

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

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

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

No survey respondents provided this information

CONCLUSION

Taurine (UNII code: 1EQV5MLY3D) was nominated for inclusion on the 503B Bulks List for a variety of indications via intravenous and intramuscular injections. Taurine is not approved in any of the national medical registries searched as a single-agent product but is available in combination with additional active pharmaceutical ingredients (API) as an intravenous product in Abu Dhabi, Australia, Belgium, Canada, the EU, Hong Kong, Ireland, Latvia, New Zealand, and the UK. Taurine is available as oral OTC natural supplements in the US and there is a current USP monograph.

From the literature review conducted, the most common indications for taurine use in both the US and non-US studies were heart failure and diabetes. Compounded products containing taurine were identified from the non-US studies, but not as the nominated intravenous or intramuscular injection.

None of the medical experts contacted reported use of taurine in practice.

From the survey responses, eight (8) out of 40 respondents used taurine. One (1) respondent reported using compounded taurine but did not specify an indication. Indications for non-compounded taurine covered a variety of disease states. According to the respondent who reported using compounded taurine, the reason to use compounded taurine over FDA-approved products is "quality," and they reported using taurine less frequently now compared to the past 5 years. No respondents reported stocking non-patient-specific compounded taurine in their practice.

APPENDICES

Appendix 1. References

- 1. Azuma J, Takihara K, Awata N, et al. Taurine and failing heart: experimental and clinical aspects. *Progress in clinical and biological research*. 1985;179:195-213.
- 2. Berger MM, Mustafa I. Metabolic and nutritional support in acute cardiac failure. *Current Opinion in Clinical Nutrition and Metabolic Care.* 2003;6(2):195-201.
- 3. Birdsall TC. Therapeutic applications of taurine. *Alternative medicine review : a journal of clinical therapeutic.* 1998;3(2):128-136.
- 4. Briganti S, Gentile M. Possibile benefit of tocotrienols in vitiligo treatment. *Pigment Cell and Melanoma Research*. 2017;30(5):e22.
- 5. Cacciapuoti F. Lowering homocysteine levels may prevent cardiovascular impairments? Possible therapeutic behaviors. *Blood Coagulation and Fibrinolysis*. 2012;23(8):677-679.
- 6. Chesney RW. Taurine: its biological role and clinical implications. *Advances in pediatrics*. 1985;32((Chesney R.W.)):1-42.
- 7. Chesney RW. Society for pediatric research presidential address. New functions for an old molecule. *Pediatric Research*. 1987;22(6):755-759.
- 8. De la Puerta C, Arrieta FJ, Balsa JA, Botella-Carretero JI, Zamarrón I, Vázquez C. Taurine and glucose metabolism: a review. *Nutrición hospitalaria : organo oficial de la Sociedad Española de Nutrición Parenteral y Enteral.* 2010;25(6):910-919.
- 9. De Luca A, Pierno S, Camerino DC. Taurine: The appeal of a safe amino acid for skeletal muscle disorders. *Journal of Translational Medicine*. 2015;13(1).
- 10. Franconi F, Di Leo MAS, Bennardini F, Ghirlanda G. Is Taurine Beneficial in Reducing Risk Factors for Diabetes Mellitus? *Neurochemical Research*. 2004;29(1):143-150.
- 11. Franconi F, Loizzo A, Ghirlanda G, Seghieri G. Taurine supplementation and diabetes mellitus. *Current opinion in clinical nutrition and metabolic care*. 2006;9(1):32-36.
- 12. Froger N, Moutsimilli L, Cadetti L, et al. Taurine: The comeback of a neutraceutical in the prevention of retinal degenerations. *Progress in Retinal and Eye Research*. 2014;41((Gaucher D.) Nouvel Hôpital civil, Hôpitaux universitaires de Strasbourg and Laboratoire de Bactériologie (EA-7290), Fédération de Médecine Translationnelle de Strasbourg, Universite de Strasbourg, France):44-63.
- 13. Imae M, Asano T, Murakami S. Potential role of taurine in the prevention of diabetes and metabolic syndrome. *Amino Acids*. 2014;46(1):81-88.
- 14. Inam u l, Piao F, Aadil RM, et al. Ameliorative effects of taurine against diabetes: a review. *Amino Acids*. 2018;50(5):487-502.
- 15. Ito T, Schaffer S, Azuma J. The effect of taurine on chronic heart failure: Actions of taurine against catecholamine and angiotensin II. *Amino Acids*. 2014;46(1):111-119.
- 16. Keith M, Errett L. Myocardial metabolism and improved outcomes after high risk heart surgery. *Seminars in Cardiothoracic and Vascular Anesthesia.* 2005;9(2):167-171.
- 17. Kendler BS. Supplemental conditionally essential nutrients in cardiovascular disease therapy. *The Journal of cardiovascular nursing*. 2006;21(1):9-16.

- 18. Manna P, Das J, Sil PC. Role of sulfur containing amino acids as an adjuvant therapy in the prevention of diabetes and its associated complications. *Current Diabetes Reviews*. 2013;9(3):237-248.
- 19. McCarty MF. Fish oil and other nutritional adjuvants for treatment of congestive heart failure. *Medical Hypotheses.* 1996;46(4):400-406.
- 20. Militante JD, Lombardini JB. Treatment of hypertension with oral taurine: Experimental and clinical studies. *Amino Acids*. 2002;23(4):381-393.
- 21. Murakami S. Role of taurine in the pathogenesis of obesity. *Molecular nutrition & food research*. 2015;59(7):1353-1363.
- 22. Omura Y. Clinical implications of the HPV-16 infection & 7 beneficial effects of optimal dose of Vitamin D3 in safe, effective cancer treatment: Non-invasive rapid cancer screening using "Mouth, Hand & Foot Writing Form" of 40 participants during 150- minute workshop on the Bi-Digital 0-ring Test, in the 1st day of European Congress for Integrative Medicine, September 9-11, 2016 in Budapest. *Acupuncture & electro-therapeutics research*. 2016;41(3-4):171-198.
- 23. Omura Y. Clinical Significance of Human Papillomavirus Type 16 for Breast Cancer & Adenocarcinomas of Various Internal Organs and Alzheimer's Brain with Increased β-amyloid (1-42); Combined Use of Optimal Doses of Vitamin D3 and Taurine 3 times/day Has Significant Beneficial Effects of Anti-Cancer, Anti-Ischemic Heart, and Memory & Other Brain Problems By Significant Urinary Excretion of Viruses, Bacteria, and Toxic Metals & Substances. Acupuncture & electro-therapeutics research. 2016;41(2):127-134.
- 24. Omura Y, Lu D, Jones MK, et al. Using new non-invasive quick method to detect Borrelia Burgdorferi (B.B.) infection from specific parts of the heart in "seemingly normal" ECGs, and from the ECGs of Atrial Fibrillation (AF), a majority of AF ECGs are found to have: 1) Significant B.B. infection, 2) Markedly increased ANP, 3) Increased Cardiac Troponin I & 4) Markedly reduced Taurine. These 4 factors were mainly localized at infected areas of the SA node area, R-&L-Atria & pulmonary veins at the L-atrium. *Acupuncture & electro-therapeutics research.* 2015;40(4):297-333.
- 25. Parcell S. Sulfur in human nutrition and applications in medicine. *Alternative Medicine Review*. 2002;7(1):22-44.
- 26. Redmond HP, Stapleton PP, Neary P, Bouchier-Hayes D. Immunonutrition: The role of taurine. *Nutrition.* 1998;14(7-8):599-604.
- Ripps H, Shen W. Review: Taurine: A "very essential" amino acid. *Molecular Vision*.
 2012;18((Shen W.) Department of Biomedical Science, College of Medicine, Florida Atlantic University, 777 Glades Road, Boca Raton, FL, United States):2673-2686.
- 28. Rusciano D, Roszkowska AM, Gagliano C, Pezzino S. Free amino acids: an innovative treatment for ocular surface disease. *European journal of pharmacology*. 2016;787:9-19.
- 29. Schaffer S, Kim HW. Effects and mechanisms of taurine as a therapeutic agent. *Biomolecules and Therapeutics*. 2018;26(3):225-241.
- 30. Schaffer SW, Jong CJ, Ito T, Azuma J. Effect of taurine on ischemia-reperfusion injury. *Amino Acids*. 2014;46(1):21-30.
- 31. Soukoulis V, Dihu JB, Sole M, et al. Micronutrient Deficiencies. An Unmet Need in Heart Failure. *Journal of the American College of Cardiology*. 2009;54(18):1660-1673.
- 32. Wu JY, Prentice H, Pan C. Neuro-protective mechanism of taurine Role of endoplasmic reticulum. *Amino Acids*. 2012;42(4):1505-1506.

- 33. Xu YJ, Arneja AS, Tappia PS, Dhalla NS. The potential health benefits of Taurine in cardiovascular disease. *Experimental and Clinical Cardiology*. 2008;13(2):57-65.
- 34. Zulli A. Taurine in cardiovascular disease. *Current Opinion in Clinical Nutrition and Metabolic Care.* 2011;14(1):57-60.
- 35. Allard ML, Jeejeebhoy KN, Sole MJ. The management of conditioned nutritional requirements in heart failure. *Heart Failure Reviews*. 2006;11(1):75-82.
- 36. Averin E. Effects of taurine during rehabilitation after CABG or valve replacement: Results of open-lable randomized trial. *European Journal of Heart Failure*. 2014;16((Averin E.) Russian State Medical University, Cardiology Department of Faculty of Postgraduate Education, Moscow, Russian Federation):258.
- 37. Azuma J, Hasegawa H, Awata N, et al. Taurine for treatment of congestive heart failure in humans. *Progress in clinical and biological research*. 1983;125((Azuma J.; Hasegawa H.; Awata N.; Sawamura A.; Harada H.; Ogura K.; Ohta H.; Yamauchi K.; Kishimoto S.)):61-72.
- 38. Azuma J, Hasegawa H, Sawamura A. Therapy of congestive heart failure with orally administered taurine. *Clinical Therapeutics*. 1983;5(4):398-408.
- Azuma J, Sawamura A, Awata N. Double-blind randomized crossover trial of taurine in congestive heart failure. *Current Therapeutic Research - Clinical and Experimental*. 1983;34(4 I):543-557.
- 40. Azuma J, Sawamura A, Awata N. Therapeutic effect of taurine in congestive heart failure: A double-blind crossover trial. *Clinical Cardiology*. 1985;8(5):276-282.
- 41. Azuma J, Sawamura A, Awata N. Usefulness of taurine in chronic congestive heart failure and its prospective application. *Japanese Circulation Journal*. 1992;56(1):95-99.
- 42. Berardo F, Ferrazza M, Roberti G, et al. Exploring the effects of an ophthalmic solution containing high concentration hyaluronic acid (0.4%) and taurine 0.5% on the ocular surface of glaucoma patients under topical hypotensive therapy. *Investigative Ophthalmology and Visual Science*. 2017;58(8).
- 43. Beyranvand MR, Kadkhodai Khalafi M, Roshan VD, Choobineh S, Parsa SA, Piranfar MA. Effect of taurine supplementation on exercise capacity of patients with heart failure. *Journal of Cardiology*. 2011;57(3):333-337.
- 44. Brøns C, Spohr C, Storgaard H, Dyerberg J, Vaag A. Effect of taurine treatment on insulin secretion and action, and on serum lipid levels in overweight men with a genetic predisposition for type II diabetes mellitus. *European journal of clinical nutrition*. 2004;58(9):1239-1247.
- 45. Darling PB, Lepage G, Leroy C. Effect of taurine supplements on fat absorption in cystic fibrosis. *Pediatric Research*. 1985;19(6):578-582.
- 46. De Carvalho FG, Galan BSM, Santos PC, et al. Taurine: A potential ergogenic aid for preventing muscle damage and protein catabolism and decreasing oxidative stress produced by endurance exercise. *Frontiers in Physiology*. 2017;8(SEP).
- 47. Giles GE, Mahoney CR, Brunyé TT, Gardony AL, Taylor HA, Kanarek RB. Differential cognitive effects of energy drink ingredients: Caffeine, taurine, and glucose. *Pharmacology Biochemistry and Behavior*. 2012;102(4):569-577.
- 48. Leuschner U. Oral bile acid treatment of biliary cholesterol stones. *Recenti progressi in medicina*. 83(7-8):392-399.

- 49. Mantovani J, DeVivo DC. Effects of taurine on seizures and growth hormone release in epileptic patients. *Archives of neurology*. 1979;36(11):672-674.
- 50. Milei J, Ferreira R, Llesuy S, Forcada P, Covarrubias J, Boveris A. Reduction of reperfusion injury with preoperative rapid intravenous infusion of taurine during myocardial revascularization. *American Heart Journal*. 1992;123(2):339-345.
- 51. Moloney MA, Casey RG, O'Donnell DH, Fitzgerald P, Thompson C, Bouchier-Hayes DJ. Two weeks taurine supplementation reverses endothelial dysfunction in young male type 1 diabetics. *Diabetes and Vascular Disease Research*. 2010;7(4):300-310.
- 52. Nebbioso M, Evangelista M, Librando A, Plateroti AM, Pescosolido N. Iatrogenic dry eye disease: An eledoisin/carnitine and osmolyte drops study. *Biomedicine and Pharmacotherapy*. 2013;67(7):659-663.
- 53. O'Donnell CP, Allott KA, Murphy BP, et al. Adjunctive taurine in first-episode psychosis: A phase 2, double-blind, randomized, placebo-controlled study. *Journal of Clinical Psychiatry*. 2016;77(12):e1610-e1617.
- 54. Pearl PL, Theodore WH, McCarter R, Drillings IM, Gibson KM. Open label trial of taurine in SSADH deficiency. *Epilepsy Currents*. 2012;12(1).
- 55. Roberti G, Agnifili L, Berardo F, et al. Prospective, Randomized, Single Masked, Parallel Study Exploring the Effects of a Preservative-Free Ophthalmic Solution Containing Hyaluronic Acid 0.4% and Taurine 0.5% on the Ocular Surface of Glaucoma Patients Under Multiple Long-Term Topical Hypotensive Therapy. *Advances in Therapy.* 2018;35(5):686-696.
- 56. Shimono KK, Azuma J, Ikeda T, et al. Temporal changes in plasma taurine level in patients with infantile spasms taking vigabatrin. *Epilepsia*. 2011;52((Nagai T.) Division of Health Sciences, Osaka Graduate School of Medicine, Suita, Japan):251.
- 57. Shiohira S, Komatsu M, Okazaki M, et al. Effect of Taurine on Hemodiafiltration in Patients With Chronic Heart Failure. *Therapeutic Apheresis and Dialysis*. 2016;20(1):20-26.
- 58. Sun Q, Wang B, Li Y, et al. Taurine Supplementation Lowers Blood Pressure and Improves Vascular Function in Prehypertension: Randomized, Double-Blind, Placebo-Controlled Study. *Hypertension*. 2016;67(3):541-549.
- 59. Wan Mahmood WA, Davenport C, King T, et al. Endothelial progenitor cell number and function, and arterial stiffness, in patients with type 2 diabetes before and after treatment with taurine: A pilot study. *Diabetes*. 2015;64((Wan Mahmood W.A.; Davenport C.; King T.; Bouchier-Hayes D.; Tun T.K.; Mcdermott J.; Sreenan S.) Dublin, Ireland, Blanchardstown, Ireland):A607.
- 60. Yoeruek E, Jägle H, Lüke M, et al. Safety profile of a taurine containing irrigation solution (AcriProTect) in pars plana vitrectomy. *Retina*. 2007;27(9):1286-1291.
- 61. Azuma J, Hasegawa H, Sawamura A. Taurine for treatment of congestive heart failure. *International Journal of Cardiology*. 1982;2(2):303-304.
- 62. Horvath GA, Hukin J, Stockler-Ipsiroglu SG, Aroichane M. Eye Findings on Vigabatrin and Taurine Treatment in Two Patients with Succinic Semialdehyde Dehydrogenase Deficiency. *Neuropediatrics.* 2016;47(4):263-267.
- 63. Horvath GA, Stockler-Ipsiroglu S, Aroichane M. Eye findings in SSADH deficiency. *Molecular Genetics and Metabolism.* 2012;105(3):325.

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 **taurine**. 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: Taurine

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **taurine**? Please check all that apply.

- □ Compounded drug product
- □ FDA-approved drug product
- \Box 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 taurine? Please check all th... != Compounded drug product

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

Display This Question:

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

Q2. Please list any conditions or diseases for which you use compounded **taurine** 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 **taurine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- \Box Single
- □ Combination

Skip To: Q5 If Do you use compounded taurine as a single agent active ingredient, or as one active ingredient...!= Combination

Display This Question:

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

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

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

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

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

Q9. Do you stock non-patient-specific compounded taurine in your practice location?

o Yes

o No

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

Display This Question:

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

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

- \Box Convenience
- \Box Emergencies
- □ Other (please describe) _____

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

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

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

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

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

End of Block: Taurine

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
- $\hfill\square$ Ophthalmology
- □ Otolaryngology
- □ Pain Medicine
- \Box Pediatrics
- □ Psychiatry
- □ Rheumatology
- □ Sleep Medicine
- Surgery (please describe) ______
- \Box Urology
- □ Other (please describe) _____

End of Block: Background Information