

Alpha Lipoic Acid

Pharmacy Compounding Advisory Committee Meeting September 12, 2018

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Alpha Lipoic Acid Review Team

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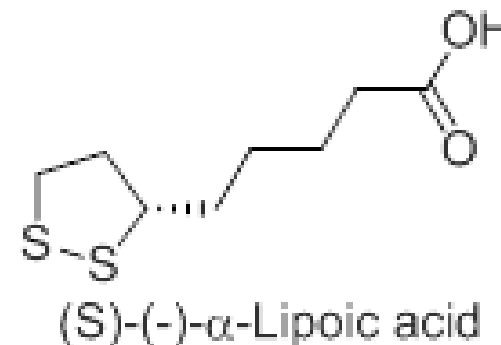
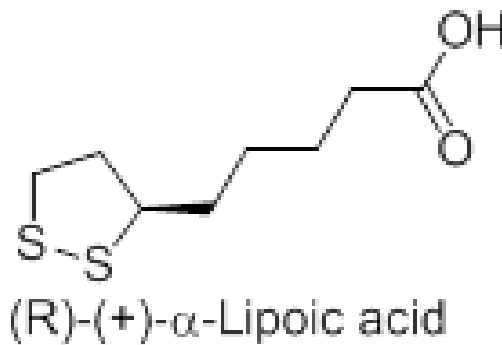
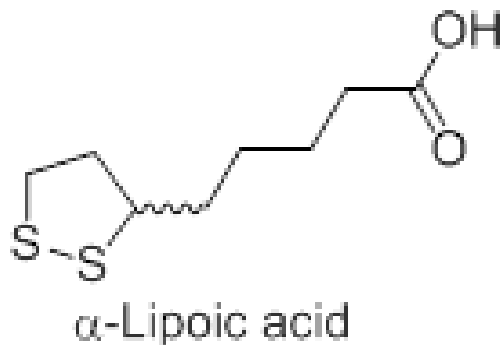
Charles Ganley, MD, Office Director, ODE4, OND

Nomination

- Proposed uses
 - Diabetic neuropathic pain
 - (Amanita) mushroom poisoning
 - Pancreatic cancer
 - Liver disease, cirrhosis (plus “toxic disease”)
 - Fibromyalgia (plus “muscle pain”)
- Proposed routes of administration
 - Oral
 - Intravenous
 - Topical

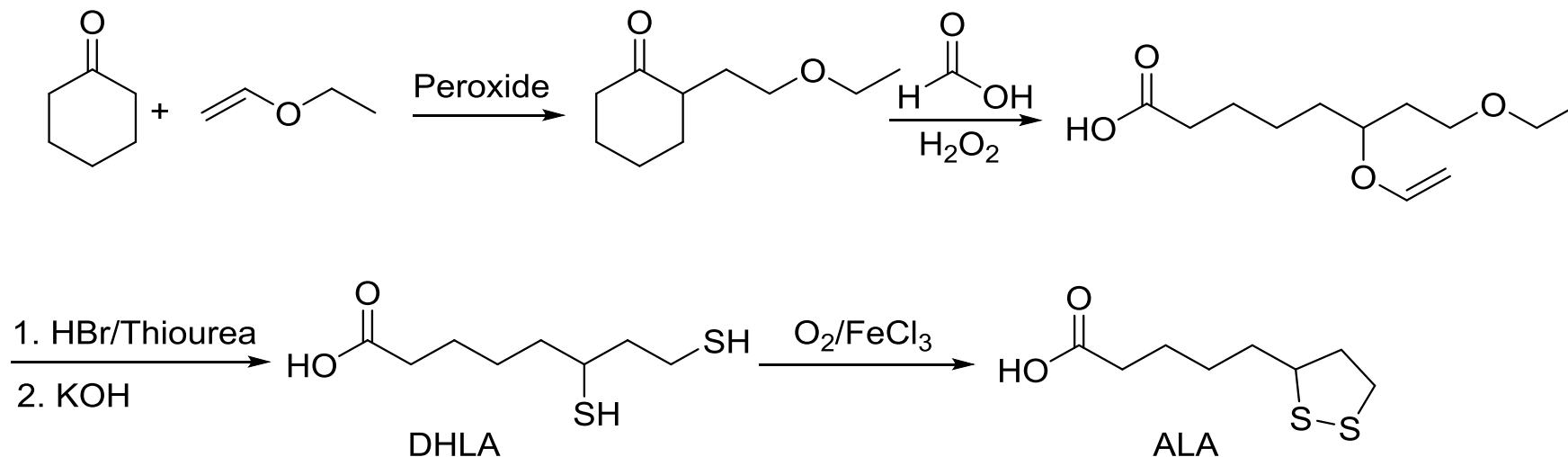
Physical and Chemical Characterization of ALA

- An 8-carbon dithiol compound derived from octanoic acid
- Part of a redox pair where the reduced form is dihydrolipoic acid (DHLA)
- R-(+) isomer is an essential cofactor for mitochondrial enzymes
- Most commercial formulations are racemic mixtures of R and S isomers
- Sensitive to light and high temperature (> 40°C)
- More stable when prepared as a solid oral formulation than a liquid formulation under normal storage conditions (room temperatures, dark containers)



Physical and Chemical Characterization of ALA (2)

- Synthesis from cyclohexanone and vinyl ethyl ether



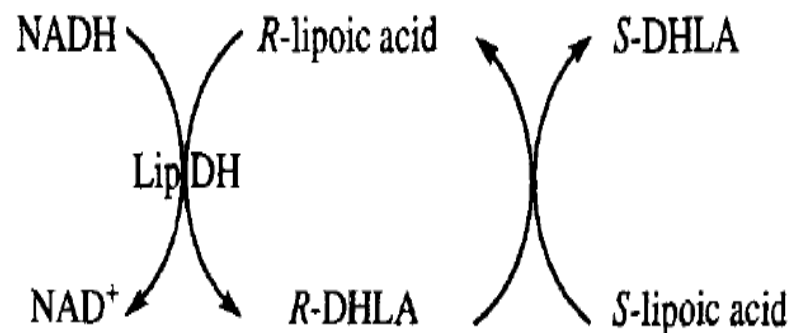
- Trace impurities are unlikely to be toxic

Conclusion:

- ALA synthesis is well characterized
- ALA is very sensitive to light and high temperatures
- ALA is stable in solid oral dosage forms; unstable in aqueous formulations

General Pharmacology of ALA

- The R form of ALA occurs naturally in all prokaryotic and eukaryotic cells
- Part of several 2-oxo acid dehydrogenases and is involved in energy production
- Transfers acyl groups from one part of the enzyme complex to another
- Is reduced to DHLA, which is re-oxidized by lipoamide dehydrogenase in the presence of NADH



NADH: Nicotinamide adenine dinucleotide disodium reduced

NAD⁺: Nicotinamide adenine dinucleotide

DHLA: Dihydrolipoic acid

LipDH: Lipoamide dehydrogenase

Nonclinical Pharmacokinetics (PK)



- ALA is absorbed quickly following oral administration in rats and dogs
- ALA exposure is dose proportional in rats and dogs
- Following absorption, ALA undergoes rapid biphasic elimination; its main metabolite, DHLA, is mostly eliminated via the urine
- When applied topically in rats, maximum skin concentrations occur within 2 hours of exposure in the stratum corneum, followed by percutaneous absorption

Nonclinical Safety



- In acute toxicity studies, the cat was the most sensitive species, followed by the monkey, dog, mouse and rat
- Route of administration impacts toxicity (intravenous was most toxic, followed by intraperitoneal, subcutaneous, and oral)
- The liver and kidney were targets of toxicity in short term studies in rats and cats
- No toxicity was seen following chronic exposure in dogs
- No data are available for reproductive/developmental toxicity
- ALA is not mutagenic in the Ames and micronucleus genotoxicity assays
- Carcinogenicity assessment was negative

ALA Clinical Safety

- No randomized clinical trial reported serious toxicity; however, most did not appear designed to rigorously collect adverse event data
- No case series reported serious toxicity, but nausea, vomiting, and vertigo reported in up to 10% of patients at doses of 1800 mg daily
- Center for Food Safety and Nutrition Center's Adverse Event Reporting System (CAERS) contained 73 case reports as of June 2018
- FDA Adverse Event Reporting System (FAERS) contained 46 individual case reports as of April 26, 2016

Effectiveness in Diabetic Neuropathy

Ten randomized controlled trials (RCTs) in patients with peripheral diabetic neuropathy

- Route of administration: oral (4 trials), intravenous (3 trials), and both oral and intravenous (3 trials) at doses from 100 to 1800 mg/day
- Primary outcome measure in six RCTs was the Total Symptom Score
- Seven of 10 RCTs and 3 meta analyses concluded that ALA modestly improved short-term neuropathic symptoms and/or nerve conduction parameters, and 3 RCTs detect no significant treatment effect
- Few trials included patients with type 1 diabetes
- No trial showed improvement in autonomic neuropathy
- No trial demonstrated long-term effect on natural history of neuropathy

Effectiveness in Amatoxin Poisoning

| Author | Time Period | Patient Survival |
|------------------------------------|----------------------|-------------------------|
| Moroni ^a | Pre-1976 | 33 of 33 (100%) |
| Nat'l Inst. of Health ^b | Aug 1974 to Nov 1978 | 67 of 75 (89%) |
| Dluholucky ^c | 1977 to 2003 | 34 of 34 (100%) |
| Fantozzi ^d | Autumn 1981 | 40 of 44 (91%) |
| Sabeel ^e | 1979 to 1994 | 19 of 19 (100%) |
| Floersheim ^f | 1971 to 1980 | 159 of 205 (78%) |
| Total | | 352 of 410 (86%) |

^aMoroni. Arch Toxicol 1976;36:111.

^bBartter. Internat Amanita Symposium Heidelberg, November 1-3, 1978.

^cDluholucky. Ces Slov Pediat 2006;61:350.

^dFantozzi. Klin Wochenschr 1986;64:38.

^eSabeel. Mycopathologia 1995;131:107.

Effectiveness in Amatoxin Poisoning (2)

- Limits to interpretation of available data
 - Inability to isolate the treatment effect
 - Use of historical controls for comparison
 - Use of exclusively IV formulations
- Current recommendations for the treatment of Amatoxin poisoning do not include ALA

Effectiveness in Pancreatic Cancer, Liver Disease and Fibromyalgia



The FDA identified no convincing reports that ALA has clinical activity or benefit in pancreatic cancer, liver disease (or cirrhosis or toxic disease), or fibromyalgia and associated muscle pain

Effectiveness Conclusion

- **Diabetic neuropathy**
Several RCTs found that ALA is associated with a modest improvement in neuropathic symptoms
- **Amatoxin poisoning**
Some but not all case series suggest that the addition of ALA to comprehensive treatment protocols increases the odds of survival with full recovery
- **Pancreatic cancer, liver disease and fibromyalgia**
FDA found no convincing reports of clinical activity

Historical Use in Compounding

- Compounding pharmacy journals suggest ALA has been compounded for at least 19 years
- Internet advertising suggests that ALA has been compounded as an injection, suppository, topical and troche formulations
- ALA is compounded for intravenous administration to treat diabetes and diabetic nephropathy
- Insufficient data are available to determine the extent of ALA use in compounded drug products

Summary

- ALA is adequately characterized chemically
- ALA may be unstable in aqueous formulations
- Available clinical reports revealed no serious safety concerns
- Clinical data suggest therapeutic potential for patients with diabetic neuropathy
- No credible evidence of meaningful clinical effectiveness in pancreatic cancer, liver disease, or fibromyalgia
- ALA appears to be compounded as an injection, suppository, topical product , and troche formulations



Recommendation

A balancing of the four evaluation criteria weighs **in favor of** ALA solid oral dosage forms being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.



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ADMINISTRATION

Coenzyme Q₁₀

**Pharmacy Compounding Advisory Committee Meeting
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Susan Johnson, PharmD, PhD
Associate Director
Office of Drug Evaluation IV
Office of New Drugs

Coenzyme Q₁₀ Review Team



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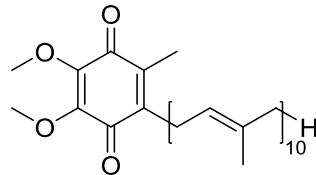
Elizabeth Hankla, PharmD, Consumer Safety Officer, OUDLC, OC

Nomination

- Coenzyme Q₁₀ has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- It is proposed for oral use in the treatment of mitochondrial disorders

Physical and Chemical Characterization

- Coenzyme Q₁₀ is a term that can refer to one of two different benzoquinone molecules
 - Each molecule has 10 isoprenoid units in the side chain
 - Ubiquinone is the fully oxidized form and ubiquinol is fully reduced form
 - Ubiquinol was previously reviewed as a bulk drug substance for the 503A list
- The nominated substance is the all-trans isomer of **ubiquinone**
 - Also called ubidecarenone
 - Commonly referred to as CoQ₁₀
- CoQ₁₀ a well characterized structure



Physical and Chemical Characterization (2)



- CoQ₁₀ is insoluble in water
 - Affects oral bioavailability
 - Compounding of intravenous formulations is not recommended
- Structure of CoQ₁₀ suggests that it would be stable under ordinary storage conditions for oral formulations
- Possible synthetic routes:
 - Chemical synthesis or semi-synthesis is feasible, but is low yield
 - Industrial production is usually via microbial fermentation

Conclusion:

- CoQ₁₀ is well characterized
- It is likely to be stable in oral formulations under normal storage conditions

General Pharmacology

- In healthy humans, CoQ₁₀ is endogenously synthesized in mitochondria
 - The total body pool of CoQ₁₀ is estimated to be 0.5 - 1.5 g
- CoQ₁₀ is found in all plants and animals, and many microorganisms
 - Humans have exogenous supply via foods; intake is 2 - 20 mg/day
- CoQ₁₀ is a
 - transporter of electrons during oxidative phosphorylation
 - generates adenosine triphosphate (ATP)
 - creates more than 90% of the energy needed by the body
 - cofactor for several mitochondrial dehydrogenases involved in fatty acid beta oxidation
 - cofactor for uncoupling proteins
 - cellular antioxidant that contributes to pyrimidine biosynthesis
 - modulator of the mitochondrial permeability pore that controls cellular apoptosis

Nonclinical Pharmacokinetics



- In rats
 - Single oral dose study of CoQ₁₀ compared the pharmacokinetics of a crystalline CoQ₁₀ formulation with several emulsion formulations
 - Time to maximum concentration (T_{max}) did not significantly differ (~ 2.5 hrs) among the various formulations
 - Area under the curve (AUC) and the maximum concentration (C_{max}) were higher with the emulsion formulations than with the crystalline formulation
 - 2-3% of orally administered dose is absorbed; human absorption is thought to be the same
- In dogs
 - Repeat dose (13 week) study showed an increase in C_{max} and AUC from day 1 through week 7, when levels plateaued

Clinical Pharmacokinetics

- Without CoQ₁₀ supplementation, normal plasma levels are 0.3 –1.48 µg/mL
 - Tissue concentrations are generally highest where energy requirements are greatest
 - Optimal concentrations have not been established
- With supplemental CoQ₁₀
 - 2 - 3% of dose is absorbed, based on animal models, and is likely both passive and active
 - Taken up by liver cells and incorporated with lipoprotein transporters
 - Enterohepatic circulation
 - 95% of ubiquinone reduced to ubiquinol based on in vitro models
 - Three compartment pharmacokinetic model is best fit
 - T_{max} is 6-8 hours after dosing
 - Distribution to peripheral tissues 6-12 hours
 - Terminal elimination half life of 33 hours
 - Steady state is reached in 3-4 weeks
 - Plasma concentration of 5 – 10 µg/mL at doses of 1200 mg/day
 - Metabolic pathways have not been well established

Nonclinical Safety



- Repeat oral dose toxicity studies did not show toxicities
 - In rabbits, no toxicities were seen with doses up to 600 mg/kg/day for 23 days
 - In rats, no toxicities were seen with doses up to
 - 1000 mg/kg/day for 4 weeks
 - 1200 mg/kg/day for 13 weeks
 - 3000 mg/kg/day for 90 days
 - 1200 mg/kg/day for 52 weeks
 - In dogs, no toxicities were seen with doses of 600 mg/kg/day after 13 weeks of dosing
- No evidence of genotoxicity in standard assay panel
- Developmental and reproductive toxicity
 - No adverse effects in pregnant rats and mice (up to 600 mg/kg/day CoQ₁₀) by oral gavage during the organogenesis stage of fetal development (gestational days 6-15)
 - No developmental studies were found in the literature
- In senescence study in mice, CoQ₁₀ did not impact lifespan or tumor formation

Clinical Safety



- Adverse Events
 - FDA Adverse Event Reporting System (FAERS)
 - 19 reports
 - 2 deaths in pediatric patients with mitochondrial disorders; both appear to be related to underlying condition
 - CFSAN Adverse Event Reporting System (CAERS)
 - 837 reports; most confounded by use of multiple supplements preventing causality assessment
 - 8 deaths reported due to stroke (n = 2), cancer (n = 2), myocardial infarction (n = 1), pulmonary embolism (n = 1), and unspecified cause (n = 2); not identified as mitochondrial disease patients
 - 22 cases in which CoQ₁₀ was only dietary supplement or drug mentioned; no apparent safety signal
 - Three clinical studies of CoQ₁₀ in healthy individuals
 - Oral dosing up to 3000 mg daily
 - Most common adverse events reported were gastrointestinal symptoms

Clinical Safety (2)



- No studies have been designed to assess the safety of CoQ₁₀ in patients with mitochondrial disorders
- Glover et al. (2010) found CoQ₁₀ treatment to be positively associated with urinary levels of 8-hydroxy-2-deoxyguanosine
 - The authors presumed this was a marker of “deleterious” oxidative stress that may be associated with higher doses of CoQ₁₀ (e.g., 1200 mg per day) taken for prolonged periods
- Remes et al. (2002) reported death of a patient on 39th day of treatment with 3 mg/kg daily of CoQ₁₀
 - Autopsy revealed cardiomyocyte degeneration and active fibrotic changes in the myocardium; not attributed to CoQ₁₀
 - Second patient died during nicotinamide crossover treatment; found to have 50% stenosis in left anterior descending coronary artery and other changes; not attributed to treatments
 - Three additional patients died shortly after the 24 month trial
 - Authors conclude that CoQ₁₀ and/or nicotinamide could be harmful in patients with severely disturbed mitochondrial function

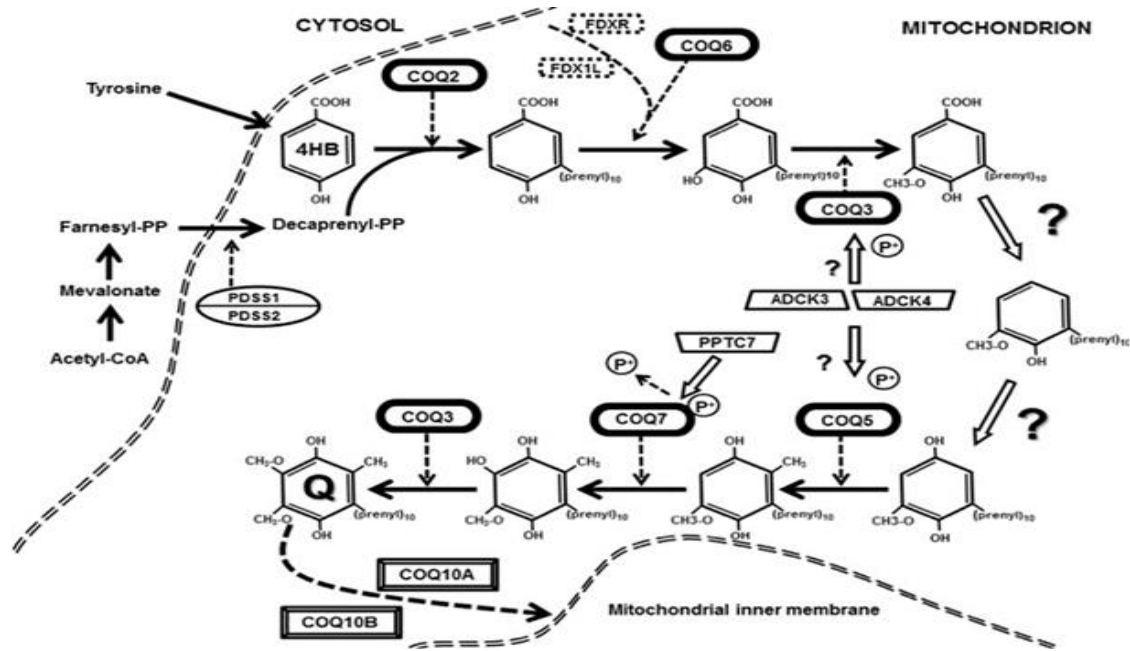
Safety Conclusion



- CoQ₁₀ appears to be associated with non-serious adverse events
 - Primarily gastrointestinal symptoms
 - Most available safety data are derived from healthy individuals
- Minimal information is available to establish safety in patients with various types of mitochondrial disorders
 - Safety profile may differ from that of healthy individuals

Synthesis of CoQ₁₀ in Mitochondria

(Acosta et al. 2016)



Effectiveness in Primary CoQ₁₀ Deficiency



- Rare disease
 - Autosomal recessive mitochondrial disorder
 - Directly related to CoQ₁₀ biosynthesis
 - Five main clinical phenotypic groups, each associated with one or more of nine genetic mutations
- Clinical improvement observed in association with CoQ₁₀ supplementation
 - No clinical trials
 - Use is recommended in Mitochondrial Medicine Society (MMS) guidelines (Parikh et al. 2015)
 - Early treatment appears key to preventing long term impairment

Effectiveness in Other Mitochondrial Disorders

- Numerous rare diseases affecting mitochondrial functions
 - Biosynthesis of CoQ₁₀ is not necessarily affected
 - Each of the many identified genetic defects is associated with various phenotypic presentations
 - Treatments are largely supportive
- One randomized, double-blind, placebo-controlled crossover study (Glover et al. 2010)
 - 60 day treatment periods separated by 70 day washout period
 - CoQ₁₀ dose of 600 mg twice daily
 - 30 patients; unequal representation of 5 different diagnoses
 - “Lack of effect on most measured variables” per authors
 - Established that systemic exposure to CoQ₁₀ increased with supplementation
- MMS guidelines
 - Evidence for use of CoQ₁₀ is “sparse”
 - Recommend that CoQ₁₀ “should be offered to most patients with a diagnosis of mitochondrial disease”

Effectiveness Conclusion



- Based on a small amount of clinical data, clinical guidelines recommend the use of CoQ₁₀ in the treatment of primary CoQ₁₀ deficiency
- There are no compelling data that establish efficacy in the support of the treatment with CoQ₁₀ of other mitochondrial diseases
 - The results of CoQ₁₀ therapy have been described in numerous publications
 - In the absence of FDA approved therapies, it is recommended by therapeutic experts in the treatment of other mitochondrial disorders
 - Data do not definitively support effectiveness for particular uses or particular doses

Historical Use in Compounding

- CoQ₁₀ has been compounded in oral and other dosage forms for a variety of medical conditions since at least 1999
- Advertised online as a component of some “mito cocktails,” which are various combinations of vitamins and dietary supplements commonly used in adults and children with mitochondrial disease
- Insufficient data are available from which to determine the extent of use of CoQ₁₀ in compounded drug products
- CoQ₁₀ is listed in the British, European, and Japanese Pharmacopeias

Recommendation



A balancing of the four evaluation criteria weighs **in favor of** coenzyme Q₁₀ for oral administration being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.



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Backup Slides



Bioavailability: Ubiquinone vs Ubiquinol



- Ubiquinol (reduced form of coenzyme Q₁₀) presented to PCAC May, 2017 for oral use as an adjunct in glycemic control
- Pharmacokinetic information for a single oral dose (180 mg) using various formulations from the same company - measured total coenzyme Q₁₀ (ubiquinol plus ubiquinone) in plasma (Miles et al. 2002)

| Formulation | C _{max} | T _{max} | C _{12 h} | AUC _{0-144 h} | AUC _{0-∞} |
|--|------------------|------------------|--------------------------|------------------------|--------------------|
| (A) Ubiquinone – solubilized* form in liquid syrup, 10 mg/mL | 1.03 ± 0.37 | 6.2 ± 1.6 | 0.51 ± 0.13 ^a | 35.82 ± 14.15 | 51.67 ± 38.01 |
| (B) Ubiquinol – in soft gel capsule, 30 mg | 1.27 ± 0.66 | 8.1 ± 6.3 | 0.55 ± 0.19 ^a | 41.09 ± 21.82 | 55.26 ± 34.53 |
| (C) Ubiquinone – solubilized* form in soft gel capsule, 30 mg | 1.03 ± 0.50 | 5.8 ± 0.7 | 0.37 ± 0.06 | 30.0 ± 9.33 | 38.80 ± 17.33 |
| (D) Ubiquinone – non-solubilized powder in hard capsule | 0.12 ± 0.05 | 6.7 ± 1.0 | 0.05 ± 0.06 | 2.81 ± 3.46 | Not assessed |

*Contains emulsifying agent and/or oil based vehicle

^a A and B are statistically different than C Control (p< 0.05); D was not included in the statistical comparisons.

Creatine Monohydrate

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Susan Johnson, PharmD, PhD
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Creatine Monohydrate Review Team



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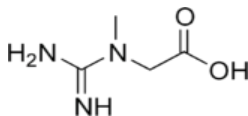
Elizabeth Hankla, PharmD, Consumer Safety Officer, OUDLC, OC

Nomination

- Creatine monohydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- It is proposed for oral use in the treatment of mitochondrial disorders
- It has also been reviewed for oral use in the treatment of creatine deficiency syndromes

Physical and Chemical Characterization

- Creatine monohydrate is a crystal form of creatine and both substances are considered the same active pharmaceutical ingredient (API)
- Creatine is a nonessential amino acid with a well characterized structure

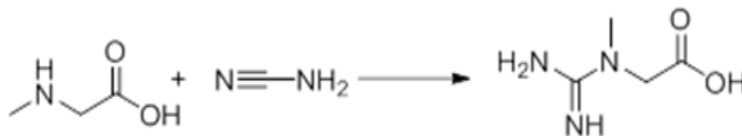


- Creatine is slightly soluble in water
- Stability
 - Likely to be stable at room temperature if kept in **solid form** and away from moisture
 - Unstable in aqueous solutions, including aqueous formulations intended for oral administration

Physical and Chemical Characterization (2)



- Possible synthetic route via a reaction between cyanamide and N-methylglycine



Conclusion:

- Creatine is well characterized
- Solid oral formulations are likely to be stable under normal storage conditions if kept away from moisture; aqueous formulations are unlikely to be stable

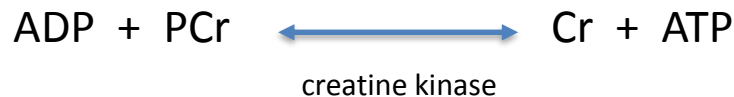
General Pharmacology

- In healthy humans, creatine is endogenously synthesized
 - Synthesized from amino acids glycine, arginine and methionine at a rate of 1 – 2 g/day
 - Process involves kidney, pancreas and liver
- Transported in plasma to target tissues
 - 95% total body pool in skeletal and cardiac muscle
 - 5% in brain, liver and other organs
- May also be ingested from meat, fish and other animal products

General Pharmacology (2)



- Creatine functions to insure energy supply to muscle:
 - When muscle is at rest, the high energy phosphate bond from adenosine triphosphate (ATP) is transferred at the mitochondrial membrane to creatine which is stored as creatine phosphate (PCr)



- During submaximal exercise, ATP is generated from adenosine diphosphate (ADP) through aerobic glycolysis
- During intense exercise, anaerobic glycogenolysis employs transfer of high energy phosphate bonds from intracellular PCr to ADP to form ATP

Pharmacokinetics



- From rodent models of oral dosing
 - Creatine is quickly absorbed from the gastrointestinal tract but has low bioavailability
 - Reaches time to maximum concentration (Tmax) within 2 hrs
 - Slowly distributed throughout the body with the highest concentrations in skeletal muscle where it is stored as PCr
- Clinical
 - Absorption is believed to involve passive and active transport through the intestinal wall
 - The portion of an orally administered dose that is absorbed is unknown
 - Plasma protein binding likely to be low due to hydrophilicity of creatine
 - Creatine transporter (CreaT) has been shown to be responsible for cellular uptake
 - Storage in muscle is saturable; excess creatine is excreted in the urine
 - Creatine in muscle is slowly metabolized to creatinine, released from muscle and eliminated in the urine
 - Approximately 2 g of creatine needs to be synthesized or ingested per day
 - No pharmacokinetics in patients with mitochondrial disorders or creatine deficiency syndromes

Nonclinical Safety



- Repeat Oral Dose Toxicity
 - 15-day toxicity study in rats and chickens (0.25 or 0.50 g/kg/day in drinking water) showed no adverse findings in histology of the liver, kidney, or skeletal muscles
 - In rodent models
 - 28-day study in rats showed no adverse findings when dosed in food up to 2 g/kg/day
 - 2 studies of renal function resulted in conflicting data; one study showed no adverse effects and the other study suggested creatine further reduced renal function in rats with pre-existing kidney disease with the human equivalent dose of 20 g/day for 1 week followed by 5 g/day for 5 weeks (a standard regimen for exercise performance enhancement with creatine dietary supplement)
 - Several studies of hepatic function in rodents resulted in conflicting data, with inflammatory changes seen in mice but not rats
- Genotoxicity
 - Ames assay was negative
 - When heated to high temperatures (e.g., food preparation grilling), creatine was mutagenic
- No developmental and reproductive toxicity data were found
- No carcinogenicity data were found

- Adverse Events
 - FDA Adverse Event Reporting System (FAERS)
 - 4 cases, including 2 serious cases
 - 42-year old male died of cardiac arrest while on hemodialysis due to acute renal failure. Patient had taken 5 g per day of creatine for an unspecified period of time, was diagnosed with diabetes, prescribed metformin and developed lactic acidosis, a potential adverse effect of metformin. It is unclear whether the patient had pre-existing diabetic nephropathy.
 - 38 year old who had been taking creatine-containing supplements for past several years was diagnosed with drug-induced cholestatic hepatitis after taking anabolic “prohormones.” Liver injury attributed to the anabolic steroids
 - CFSAN Adverse Event Reporting System (CAERS)
 - 139 reports including 4 deaths, each apparently unrelated to creatine use
 - 8 reports in which creatine supplements were the only substance that the patient was reported to have taken; no serious events and no renal toxicity

Clinical Safety (2)



- Clinical studies
 - No serious adverse events were reported in studies of patients with mitochondrial disease
 - No studies in patients with creatine deficiency syndrome
- Published adverse event cases
 - One case report of urinary crystals being observed in a creatine deficiency syndrome patient taking doses of 800 mg/kg/day; resolved with dose reduction
 - 18 year old male with mitochondrial disease and preexisting nephropathy, who had been given 20 g creatine daily for 12 days, then 5 g daily for 28 months, experienced increased renal insufficiency with urea retention and impaired creatinine clearance. Decline was associated with underlying disease but clinician authors recommend use of creatine with caution in patients with mitochondrial disease.

Clinical Safety (3)



- **Creatine renal toxicity review** (Gualano et al. 2012)
 - Numerous published cases and anecdotes between late 1990s and 2012; many associated with use of creatine in healthy individuals for the purpose of enhanced athletic performance and muscle strength
 - Doses of approximately 2-5 g/day over a period of months does not appear to be associated with renal toxicity in patients with normal renal function
 - Higher doses (>5 g/day) are not recommended for chronic use
 - Special populations, including those with disease states that may affect renal function, have not been adequately studied

Safety Conclusion



- In healthy adults, creatine appears to be generally associated with non-serious adverse events
 - Urinary crystals were observed at doses of 800 mg/kg/day in a creatine deficiency syndrome patient
- Clinical data may support the potential for creatine to cause renal toxicity particularly in patients who have, or are at risk of, renal impairment.
 - Observed inconsistently in nonclinical data
 - Mitochondrial disorders are often associated with renal impairment

Effectiveness in Creatine Deficiency Syndromes



- Rare diseases
 - Autosomal recessive inborn genetic errors
 - Result in diminished brain pool of creatine based on magnetic resonance spectroscopy (MRS) assessment and related cognitive and functional disabilities
 - Distinct from mitochondrial disorders
 - Two syndromes are due to enzyme deficiencies in creatine synthesis process
 - L-arginine-glycine amidinotransferase (AGAT) deficiency; review in 2015 reported 16 patients in 8 families worldwide
 - Guanidinoacetate methyl-transferase (GAMT) deficiency; review in 2014 reported 48 patients in 38 families worldwide
 - No prospective clinical trials
 - No FDA approved drugs for this indication
 - Used doses up to 800 mg/kg/day, creatine has been documented to increase brain creatine levels and improve symptoms
 - Differing views on use in CreaT transporter deficiency

Effectiveness in Mitochondrial Disorders

- Rare diseases involving various functions of mitochondria
 - Numerous identified genetic defects, each responsible for various phenotypic presentations
 - No approved FDA drugs; treatments are largely supportive
- Three placebo-controlled crossover studies
(Tarnopolsky et al. 1997, Klopstock et al. 2000, Kornblum et al. 2005)
 - Use of exercise performance metrics (strength, torque, plasma lactate, etc)
 - Minor improvement on subset of endpoints in first study only during high-intensity aerobic and anaerobic activities; not replicated
 - Dosing up to 20 g creatine per day; creatine plasma levels were shown to have increased during treatment
- Mitochondrial Medicine Society guidelines
 - Do not provide a recommendation for the use of creatine

Effectiveness Conclusion

- Based on a small amount of clinical data, creatine is used in the treatment of creatine deficiency syndromes, AGAT deficiency and GAMT deficiency
- There are no compelling data that establish efficacy in the support of creatine treatment of mitochondrial diseases

Historical Use in Compounding

- Insufficient data are available from which to determine how long creatine has been used in compounded drug products and the extent of use
- Advertised online as a component of some “mito cocktails,” which are various combinations of vitamins and dietary supplements commonly used in adults and children with mitochondrial disease
- Creatine is not listed in the British, European, and Japanese Pharmacopeias

Recommendation



A balancing of the four evaluation criteria weighs **in favor of** creatine monohydrate solid oral dosage forms being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.



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Backup Slides



Stability of Creatine in Solution

- Based on published literature, stability concerns are most prominent at low pH (e.g., pH 1.5 – 4)
(References Edgar 1925 and Cannan 1928)
- Degradation also occurs in solution at higher pH (e.g., pH 6 – 7)
 - Degradation process is slower
 - Relevant to compounded formulations

Pyridoxal-5-Phosphate Monohydrate

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Office of New Drugs

Pyridoxal-5-Phosphate Monohydrate Review Team

The logo of the U.S. Food and Drug Administration (FDA), consisting of the letters "FDA" in white on a blue square background.

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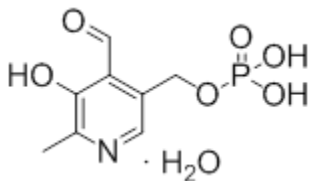
Nomination

- Pyridoxal-5-phosphate monohydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- It is proposed for oral and intravenous use in the treatment of epilepsy and seizure disorders

Physical and Chemical Characterization



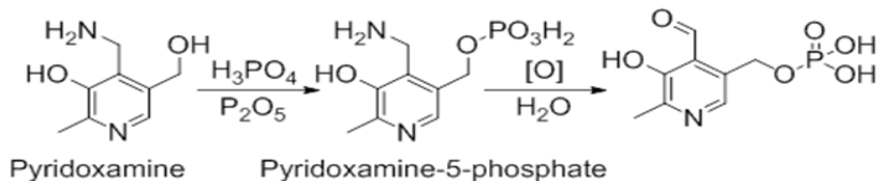
- Pyridoxal-5-phosphate monohydrate and pyridoxal-5-phosphate (PLP) are considered the same active pharmaceutical ingredient (API)
- PLP has a well characterized structure



- PLP is soluble in water

Physical and Chemical Characterization (2)

- Stability
 - In aqueous solution, PLP is stable at neutral and weak acidic or alkaline conditions (pH 5.0 – 8.0) up to 98°C
 - No stability issues were found in association with the solid form of PLP
- PLP can be synthesized from pyridoxamine



Conclusion:

- PLP is well characterized
- It is likely to be stable under normal storage conditions as oral or intravenous dosage forms
- Aqueous dosage forms will be most stable at neutral and weak acidic or alkaline conditions

General Pharmacology

- Vitamin B₆ is comprised of 6 structurally related compounds (vitamers)
 - Pyridoxal (PL), pyridoxine (PN), and pyridoxamine (PM) PLUS their phosphorylated esters PNP, PMP and PLP
 - They can be interconverted in the human body
- PLP is the metabolically active form of vitamin B₆
- PLP is an essential cofactor for at least 140 different enzymatic reactions
 - Amino acid metabolism
 - Heme and neurotransmitter synthesis
 - Metabolism of glycogen, lipids, steroids, vitamins
 - Conversion of tryptophan to niacin
- PLP is found in animal food sources
 - FDA recommends a tolerable upper limit of 100 mg/day of vitamin B₆ in food

Pharmacokinetics



- No nonclinical pharmacokinetic data were found for PLP
- With oral ingestion in healthy humans
 - Generally, only non-phosphorylated vitamers are absorbed
 - Vitamers that are phosphorylated when ingested (PNP, PMP and PLP) are hydrolyzed by intestinal phosphatases
 - The non-phosphorylated forms (PN, PM and PL) are rapidly absorbed (40% of dose in 10 minutes for PL) using an energy dependent process
 - Following absorption, PN, PM and PL are phosphorylated, a reaction catalyzed by pyridoxal kinase, found primarily in the liver
 - PNP and PMP are converted to the metabolically active form, PLP, via pyridoxine-5-phosphate oxidase, also known as pyridoxamine-5-phosphate oxidase or PNPO
- At high doses, PLP is absorbed without being hydrolyzed, reducing the dependence on PNPO conversion of PNP and PMP to PLP

Pharmacokinetics (2)

- Following oral administration of a 100 mg dose of PN, PM or PL, most is excreted unchanged in urine by 36 hours after dosing (Ink and Henderson 1984)
- Drugs interactions
 - Drugs that can react with carbonyl groups have the potential to interact with PLP: isoniazid, L-dopa
 - Women using high-dose oral contraceptives may have decreases in vitamin B₆ status indicators

- No toxicity data were found specific to PLP
- For vitamin B₆
 - Repeat dosing of high doses results in neuronal damage and sensory and motor effects in multiple species; dose and duration dependent
 - Developmental and reproductive toxicity in rats
 - Vitamers have been shown to cross the placenta barrier and reach the fetus
 - Decreased weight of the epididymides and decreased number of sperm in rats dosed with vitamin B₆ for 6 weeks (IP injection of 125-1000 mg/kg/day)
 - When dosed between gestation days 6-15 (IP injection of 20-80 mg pyridoxine/kg/day), no teratogenicity was seen
 - At higher doses ≥ 400 mg/kg, there was a significant decrease in body weight of pups
 - No genotoxicity or carcinogenicity studies were found

- Adverse Events
 - FDA Adverse Event Reporting System (FAERS)
 - 20 cases for PLP; 12 cases are likely related to concomitant medication or underlying disease
 - In 8 cases, including 6 deaths, limited information did not provide sufficient details to assess causality
 - CFSAN Adverse Event Reporting System (CAERS)
 - 98 reports for PLP; no deaths
 - Use of multiple ingredient supplements was reported in each case and confounded causality assessment
 - Clinical studies
 - No studies designed to assess safety
 - Literature reports of neuronal damage and sensory and motor effects with vitamin B₆ at high doses; can be expected to occur with PLP as well
 - At high doses, PLP can interfere with platelet function
 - Dermatologic, gastrointestinal and hepatic events have been reported

Safety Conclusion



- PLP is generally safe and well tolerated
- With prolonged high doses, it may be associated with peripheral nerve injury
- Dermatologic, gastrointestinal and hepatic events have been reported

Effectiveness



- Pyridoxal-5-phosphate (PLP) dependent epilepsy
 - Caused by enzyme deficiency of PNPO
 - Autosomal recessive rare disease due to inborn error of metabolism, a mutation in the PNPO gene
 - Onset is generally within the first 2 weeks of life
 - Myoclonic seizures that may become status epilepticus
 - Patients are often encephalopathic
 - Not responsive to anticonvulsants or to pyridoxine (in patients with residual PNPO function)
- Oral administration of PLP at high doses
 - Results in cessation of seizures quickly and contributes to confirmation of diagnosis
 - Multiple published treatment guidelines and case studies
 - Doses of 10 – 100 mg/kg/day divided into 4 – 6 doses as oral suspension
 - Treating disorder early in life is the key to avoiding irreversible neurologic damage
- Generally not recommended for treatment of adult seizures, but related research is ongoing

Effectiveness Conclusion

- PLP is effective for treating PLP dependent epilepsy in neonates and infants caused by PNPO deficiency



Historical Use in Compounding

- PLP has been used in pharmacy compounding since at least 2010 in oral suspension, injectable, and transdermal dosage forms
- PLP is known to be compounded to treat PLP-dependent epilepsy and as adjunct therapy for autism spectrum disorders
- Insufficient data are available from which to determine the extent of use of PLP in compounded drug products
- PLP is not listed in the British, European, or Japanese Pharmacopeias

Recommendation



A balancing of the four evaluation criteria weighs **in favor of** pyridoxal-5-phosphate monohydrate oral and intravenous dosage forms being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.



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ADMINISTRATION

Quercetin Dihydrate

**Pharmacy Compounding Advisory Committee Meeting
September 12, 2018**

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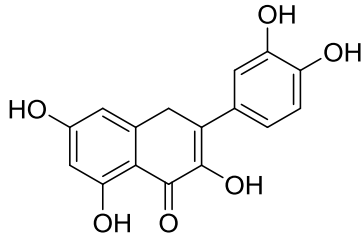
Elizabeth Hankla, PharmD, Consumer Safety Officer, OUDLC, OC

Nomination

- Quercetin dihydrate has been nominated for inclusion on the list of bulk drug substances for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Proposed uses:
 - Asthma
 - Allergy
 - Hypertension
 - Cancer prevention and treatment
- Proposed routes of administration:
 - Oral
 - Sublingual
 - Intravenous
 - Intramuscular

Physical and Chemical Characterization

- Quercetin is a naturally occurring flavonol found in fruits and vegetables
- It is a yellow crystalline solid chemical with a well characterized structure



- Quercetin exists in different crystalline forms based on the degree of hydration
- It is stable in its solid form when protected from oxygen

Physical and Chemical Characterization (2)

- Quercetin **dihydrate** is the most thermodynamically stable hydrate form which may contribute to a lower bioavailability
- It is less stable in aqueous solutions due to rapid oxidation and other degradations under basic conditions and is unlikely to be stable when compounded as aqueous solutions
- Possible synthetic route: Extraction from plant tissues
 - Rapid extraction from powdered quercetin bark with dilute ammonia and boiling of the extract with sulfuric acid

Physical and Chemical Characterization (3)

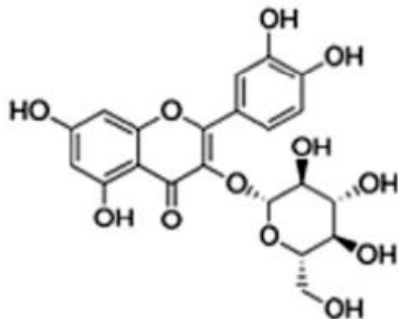
Summary

- Quercetin is a naturally occurring, well characterized flavonol
- Quercetin extraction and synthesis is well developed
- It is likely to be stable in a solid form when protected from oxygen, but not in aqueous formulations
- Quercetin dihydrate is the most thermodynamically stable hydrated form which may affect the bioavailability

General Pharmacology



- The average quercetin dietary intake from food sources for humans ranges from 25-205 mg/person/day; in some individuals with high intake of fruit and vegetables it may increase to 1250 mg/day
- In its natural form in food, quercetin exists as quercetin glycoside or rutinoides
- Approximately 150 glycosides of quercetin have been described and includes mono-, di-, or oligosaccharides



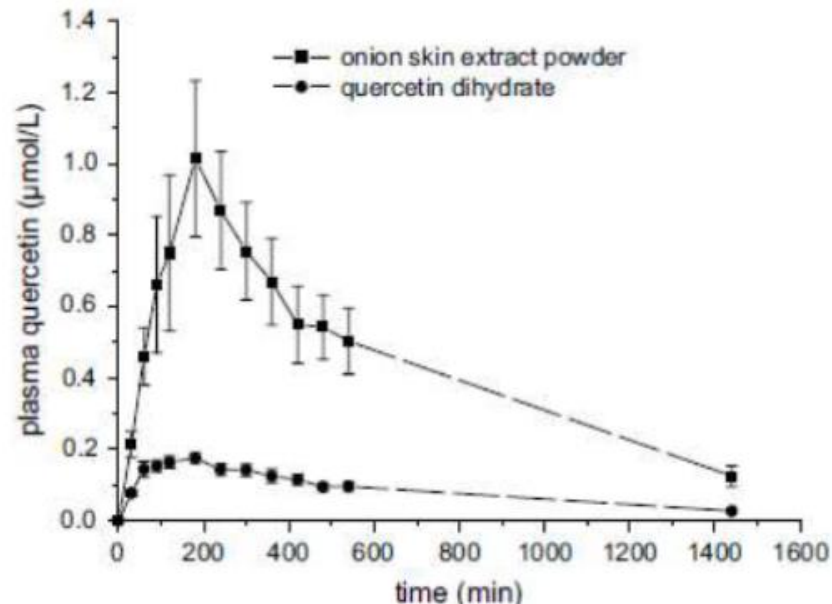
General Pharmacology (2)



- In the gut, quercetin glycosides are converted to quercetin aglycone and sugar moieties; this is important because quercetin is lipophilic while the glycoside forms are polar
- Based on in vitro and in vivo models, quercetin may act as an antioxidant, anti-inflammatory, anti-proliferative, anti-angiogenic agent; many of these models are conducted with quercetin aglycone and not quercetin metabolites

Pharmacokinetics

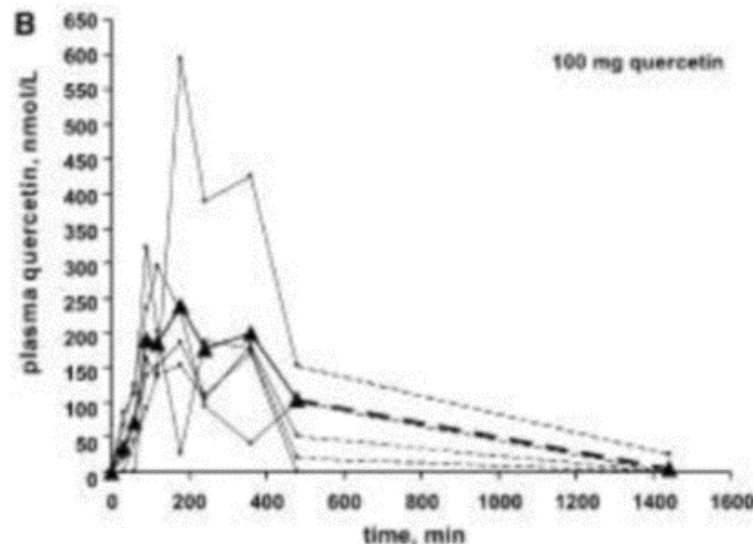
- The bioavailability of quercetin is generally poor and variable
- For solid dosage formulations, the chemical form of quercetin makes a difference
- In a study comparing absorption of quercetin from quercetin dihydrate and onion skin extract, the bioavailability of quercetin was greater with the extract (Burak et al. 2017)



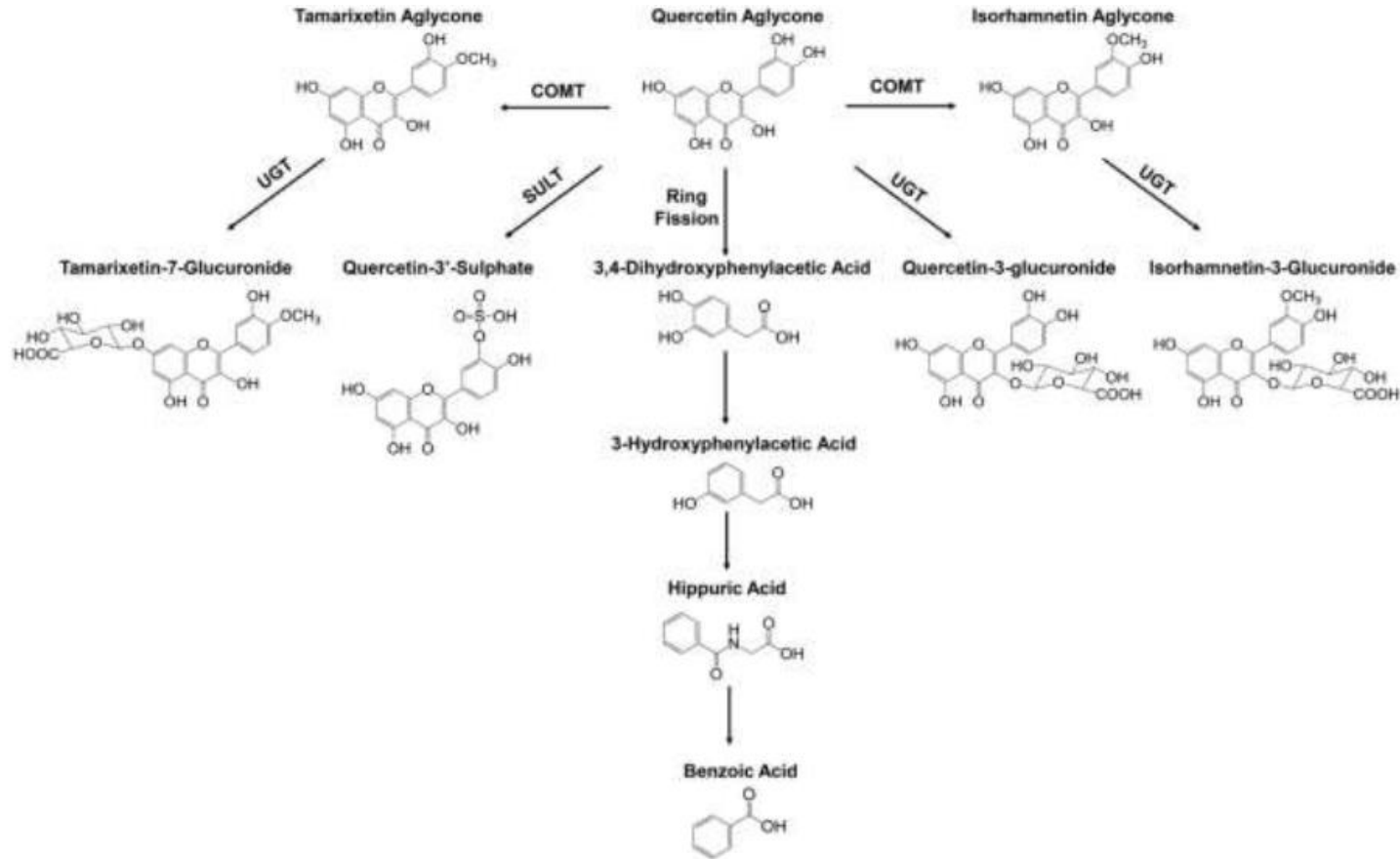
Pharmacokinetics (2)



- Elimination of quercetin is via conjugation reactions or ring fission to eventually produce benzoic acid which is excreted in the kidneys
- Conjugation occurs quickly in the intestinal cell; the aglycone form undergoes glucuronidation, sulfation and methylation; these are the primary forms of circulating quercetin
- Conjugated forms have little or no activity
- Conjugated forms excreted in the bile fluid can undergo enterohepatic circulation



Pharmacokinetics: Metabolism



Pharmacokinetics (4)



- Various foods and drinks can affect quercetin absorption
- There are potential drug interactions through different mechanisms
 - Quercetin interacts with different CYP P450s that have not been fully characterized (e.g. 2C9, 1A2, 2C19, 2D6)
 - Quercetin may enhance or inhibit the transport of P-glycoprotein substrates (e.g. vincristine) depending on the concentration of quercetin

Nonclinical Safety



Acute toxicity

- There is limited data on the acute toxicity of quercetin; observational studies were limited to animal symptoms without histopathology

Repeat Dose toxicity

- No toxicities seen in rabbits for orally fed quercetin (1%) for 410 days
- In a 2-year rat carcinogenicity study, increased severity of chronic nephropathy, slight increase in focal hyperplasia of the renal tubule epithelium and an increased incidence of parathyroid hyperplasia were seen in males at $\geq 10,000$ ppm
- A 6-month interim report of the 2-year study showed reduction in body weight among females (40,000 ppm) and increases in relative kidney and liver weights in both sexes (40,000 ppm)

Nonclinical Safety (2)

- Genotoxicity
 - Positive genotoxic signal for in vitro studies (Ames, chromosomal aberrations and sister chromosome aberrations)
 - Negative genotoxic signal for in vivo studies (micronuclei, sister chromatid exchange)

- Developmental and reproductive toxicity
 - No adverse effects reported in the literature

- Carcinogenicity
 - Oral administration of quercetin (0.1% in diet for 540 days) in rats did not increase the incidence of tumor formation when compared to concurrent controls

Clinical Safety



FDA Adverse Event Reporting System (FAERS)

- 7 reports submitted to FDA for an FDA approved drug included concomitant use of quercetin
- Attribution to quercetin not possible because of multiple concomitant drugs or limited information
- One report of possible interaction with apremilast (metabolized by CYPs with subsequent glucuronidation)

CFSAN Adverse Event Reporting System (CAERS)

- 20 reports: 7 hospitalizations reported; none appear to be directly related to taking quercetin.
- Majority of cases were confounded by multiple medications and/or underlying disease or there was insufficient information for assessment.

Clinical Safety (2)

- No adverse events reported in clinical trials for orally administered quercetin
- No safety related case reports were found in the literature
- Serious adverse events occurred after administration of high dose intravenous quercetin to patients with cancer including:
 - Pain at the site of injection ($\geq 60 \text{ mg/m}^2$)
 - Dyspnea ($\geq 1400 \text{ mg/m}^2$)
 - Vomiting ($\geq 1700 \text{ mg/m}^2$)
 - Significant renal toxicity ($\geq 630 \text{ mg/m}^2$; some patients had residual renal injury after treatment stopped)
- Drug-drug interaction studies:
 - Quercetin significantly induced CYP3A activity to substrate midazolam and the induction was partly related to CYP3A5 genotype
 - Quercetin isolated from St. John's Wort has been shown to inhibit activities of cytochromes 1A2, 2C19 and 2D6

Clinical Effectiveness

Cancer prevention and treatment

- There are mechanistic in vitro studies, sporadic small clinical studies and extensive literature on purported mechanisms for treating a wide variety of cancer, but no compelling clinical studies evaluating effectiveness
- For prevention, there are no clinical studies and most information is based on dietary intervention with multiple dietary ingredients. None of which is supportive of use to prevent cancer

Allergy

- Most clinical studies conducted to date have evaluated combinations or mixtures of ingredients either in the form of an herbal product or in a food substance. There is insufficient data from clinical studies to support the effectiveness of quercetin in the treatment of allergy

Clinical Effectiveness (2)

Hypertension

- In a meta-analysis of available randomized controlled trials evaluating the impact of quercetin on blood pressure (BP), the authors suggested a statistically significant effect of quercetin supplementation in the reduction of BP when used at doses higher than 500 mg/day
 - However, in evaluating each study in the meta-analysis, we did not find a single study that showed a significant effect on blood pressure compared to placebo
 - In the studies reporting a statistically significant effect on blood pressure, the authors conducted within treatment comparisons (baseline minus end-study visit) and not between treatment comparisons; the change in blood pressure for quercetin versus placebo did not show a significant difference

Asthma

- No clinical studies where quercetin was administered and evaluated for the treatment of asthma were found



Clinical Effectiveness: Conclusion

- There is insufficient data to support the effectiveness of quercetin in the treatment of cancer, allergy, hypertension or asthma

Historical Use in Compounding

- Insufficient information is available to determine how long quercetin has been used in pharmacy compounding
- Insufficient data are available from which to draw conclusions about the extent of use of quercetin in compounded drug products
- Quercetin is not listed in the British, European or Japanese Pharmacopeias

Recommendation

Chemistry

- Quercetin dihydrate is well characterized and stable in a solid dosage form if protected from oxygen
- It is likely to be unstable in aqueous solutions and readily undergoes oxidation

Safety

- With oral administration, there appear to be no serious adverse effects; for intravenous administration, serious adverse events include dyspnea, vomiting and kidney toxicity
- Oral absorption is poor and variable
- There is rapid metabolism to glucuronides and sulfates which raise questions about the bioavailability of quercetin aglycone
- There are potential interactions with CYP enzymes that have not been fully explored which raise concerns about potential drug interaction if used with approved drug products that are metabolized by CYP enzymes; there may be interactions with transporters

Recommendation (2)

Effectiveness

- There is insufficient data to support the effectiveness of quercetin in the treatment of cancer, allergy, hypertension or asthma

Historical Use in Compounding

- Insufficient data are available from which to draw conclusions about the extent of use of quercetin in compounded drug products

Recommendation (3)

- A balancing of the four evaluation criteria weighs **against** quercetin dihydrate being added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.



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