

# **Introductory Remarks**

## **Pharmacy Compounding Advisory Committee**

### **October 27, 2015**

**Jane A. Axelrad**  
**Associate Director for Policy**  
**Center for Drug Evaluation and Research**  
**And Agency Lead on Compounding**

## What have we covered so far?

- 29 candidates for the withdrawn/removed list; two modifications to current list
- Criteria for the 503A bulks list
- 10 substances nominated for inclusion on the 503A bulks list
- Criteria for the difficult to compound list

## 503A Bulk Drug Substances

A licensed pharmacist or licensed physician can compound a drug product under section 503A using bulk drug substances that:

- Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;
- If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or
- If such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A. (See section 503A(b)(1)(A)(i) of the FD&C Act).

# Topics For Discussion At This Meeting

- 9 bulk drug substances nominated for the 503A list

## Background Information

- Draft guidances on 503A and 503B bulk drug substances interim policy
- Botanical drugs
- Dietary supplements

## Update: Interim Policy Re Compounding With Bulk Drug Substances While Lists Are Being Developed

- Two draft guidances issued yesterday:
  - Compounding using bulk drug substances under section 503A in the interim while the 503A bulk drug substance list is being developed
  - Compounding using bulk drug substances under section 503B in the interim while the 503B bulk drug substance list is being developed

## Each draft guidance references four lists which also published

- List 1: Bulk drug substances under evaluation;
- List 2: Bulk drug substances that raise safety concerns;
- List 3: Bulk drug substances nominated without adequate support; and
- List 4: Bulk drug substances that may not be used to compound drug products (to be developed).
- 503A and 503B have the same four categories of interim lists but lists include different drugs because different criteria, different substances nominated, and different processes for developing the bulks lists under 503A and 503B

## Interim Policy – 503A

- Until the substance has been considered and dealt with in a final rule as being included, or in the preamble of the final rule as not included on the 503A bulks list, FDA does not intend to take action against a compounder under section 503A that is compounding with bulk drug substances on List 1 provided that several conditions are met.
- List 1 includes substances nominated with sufficient supporting information for FDA to evaluate them and that have not been identified by FDA as a substance that appears to present safety concerns (which are listed on List 2).

## 503B Bulk Drug Substances

- An outsourcing facility must not compound drug products using a bulk drug substance unless:
  - (1) the substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need (see section 503B(a)(2)(A)(i)) of the FD&C Act, or
  - (2) the drug product compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing (see section 503B(a)(2)(A)(ii) of the FD&C Act).



## Interim Policy – 503B

- Until FDA publishes its final determination in the Federal Register that a bulk drug substance may or may not be used in compounding under section 503B, FDA does not intend to take action against an outsourcing facility that is compounding a drug product using a bulk drug substance that appears on List 1.
- List 1 includes substances nominated with sufficient supporting information for FDA to evaluate them and that have not been identified by FDA as a substance that appears to present safety concerns (which are listed on List 2).

## FDA Reopening Dockets for New Nominations

- FDA established two public dockets (one for 503A and one for 503B) where
  - substances can be re-nominated with sufficient supporting information or
  - new nominations can be submitted of bulk drug substances that were not previously nominated
- FDA will consider re-nominated and new substances after completing the reviews of the substances that have already been determined to have been supported with sufficient information to evaluate them.

## USP dietary supplement monographs are not “applicable monographs” under section 503A

- A bulk drug substance is defined, in part, as a substance that “becomes an active ingredient or a finished dosage form of the drug, but does not include intermediates used in the synthesis of such substances” (see section 503A(b)(1)(A) and 21 CFR 207.3(4)).
- A dietary ingredient or dietary supplement used to compound a drug is considered a drug, and the “applicable” USP or NF monographs are those applicable to drugs



# **Dietary Supplements**

**Pharmacy Compounding Advisory Committee  
Meeting  
October 27, 2015**

**Brad Pace  
Chief, Health Fraud Branch  
Office of Compliance  
Center for Drug Evaluation and Research (CDER)**

# Introduction

- Whether a product is regulated as a drug or dietary supplement depends on several factors, including, but not limited to:
  - ingredient(s)
  - route of administration
  - intended use
- A firm that produces dietary supplements must follow all dietary supplement legal requirements, including labeling and CGMPs.

# What is a dietary supplement?

- Under section 201(ff) of the FD&C Act, a dietary supplement is a product that:
  - is intended to supplement the diet
  - contains one or more dietary ingredients
  - is intended for ingestion
  - is not represented for use as a conventional food or as a sole item of a meal or the diet
  - is labeled as a dietary supplement
- Certain articles studied under an IND or approved as new drugs are not permitted in dietary supplements under section 201(ff)(3) of the FD&C Act.

# What is a dietary ingredient?

A dietary ingredient is:

- a vitamin,
- a mineral,
- an herb or other botanical,
- an amino acid,
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or
- a concentrate, metabolite, constituent, extract, or combination of any of the above ingredients.

# Certain ingredients are not permitted in dietary supplements

Except in cases when the ingredient was marketed as a food or supplement prior to the approval or authorization, a dietary supplement cannot contain:

- active ingredients in approved new drugs, or
- active ingredients in products authorized for investigation (i.e., INDs) with substantial clinical trials that have been made public.



# Route of Administration

- Dietary supplements must be intended for ingestion
  - i.e., tablet, capsule, powder, softgel, gelcap, or liquid form
- Dietary supplements cannot be, for example, sublingual, injectable, topical, or nasal

# Intended Use

- A dietary supplement can include claims to affect the structure or function of the body (structure/function claims).
- A dietary supplement cannot include claims stating or implying that the product will diagnose, mitigate, treat, cure or prevent disease (disease claims).
- If a product intended for ingestion is marketed with disease claims, it would be subject to regulation as a drug.

<b>Structure / Function Claims → Dietary Supplement</b>	<b>Disease Claims → Drug</b>
<ul style="list-style-type: none"> <li>- Supports the immune system</li> <li>- Promotes mental alertness</li> </ul>	<ul style="list-style-type: none"> <li>- Relief of bronchospasm (asthma)</li> <li>- Treats or prevents Alzheimer's</li> </ul>

# Dietary Supplement CGMPs

- All firms that produce dietary supplements must register with FDA and are subject to dietary supplement CGMPs.
- The dietary supplement CGMP rule in 21 CFR part 111 applies to all firms that manufacture, package, label or hold dietary supplements.
- Compliance is monitored by FDA inspection.

# Examples

- Product X contains green tea extract, is intended for topical use, includes the statement “dietary supplement,” and is marketed to maintain healthy joints.
  - Product X is subject to regulation as a drug because it is not ingested
- Product Y contains beta carotene, is intended for ingestion, and is marketed to prevent Alzheimer's.
  - Product Y is subject to regulation as a drug because it makes a disease claim
- Product Z contains echinacea, is intended for ingestion, includes the statement “dietary supplement,” and is marketed for mental alertness.
  - Product Z could be marketed as a dietary supplement as long as the firm meets all other legal requirements for dietary supplements.

# Multiple Ingredient Products

A dietary supplement cannot be legally marketed if it combines dietary ingredients with certain drug ingredients studied under IND or approved as new drugs under 201(ff)(3)(B) of the FD&C Act.

## Example

- Product A contains beta carotene and ibuprofen, is marketed for ingestion, includes the statement “dietary supplement,” and is intended to maintain healthy joints.
  - Subject to regulation as a drug because the product contains ibuprofen, which is the active ingredient in various FDA approved drugs and which was not marketed as a food or supplement prior to approval.



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

[www.fda.gov](http://www.fda.gov)

# Botanical Drug Development and Quality Standards

**Pharmacy Compounding Advisory Committee  
Meeting  
October 27, 2015**

**Sau (Larry) Lee, PhD  
Acting Associate Director for Science  
Botanical Review Team Leader  
Office of Pharmaceutical Quality**

# What are the botanical drugs?

- The term *botanical* means products that include plant materials, algae, macroscopic fungi, or combinations of these.
  - It excludes highly purified drug substances, products containing animals or animal parts and or minerals, materials derived from botanical genetically modified species, and fermentation products
- Botanical drugs can be available as (but not limited to) a solution, powder, tablet, capsule, topical, or injectable.



## FDA has approved two botanical NDAs

- Veregen: a topical drug from green tea catechins for the treatment of genital warts
- Fulyzaq: an oral drug for the treatment of HIV/AIDS related diarrhea





# Botanical Drug Characteristics

- Heterogeneous mixtures that contain
  - Multiple chemical components
  - Potentially more than one chemical component that contributes meaningfully to the mixture's physiological or pharmacological action
- Chemical components and their biological activities are generally not well characterized.
- Exhibit batch-to-batch variations in properties (e.g., chemical composition)
  - Natural variability at the plant and raw material levels
  - Greater than the variability typically observed in non-botanical drugs (e.g., chemically synthesized and purified drug molecules)

# Scientific and Regulatory Challenges

- Botanical drugs are complex
  - Multiple chemical components
  - Not well-defined active component(s)
  - Natural variations
- New botanicals intended to be marketed as FDA-approved drugs in the US are expected to meet the same standards as non-botanical drugs for quality, safety, efficacy
  - **A conventional quality control approach for small-molecule drugs (mainly based on chemical testing) under the NDA pathway is insufficient for quality control of botanical products**
  - Information on prior human use may provide some indication of the safety profile of botanical products for early phase trials
  - Late-phase clinical studies should be designed to assess the effect of batch-to-batch variations on the efficacy of botanical products

# Integrated Approach to Quality Control of Botanical Drugs

- To ensure the marketed product batches deliver a therapeutic effect consistent with that observed for product batches tested in the clinical studies (i.e., therapeutic consistency):
  - **Raw Material Control:** cultivar control; good agricultural and collection Practices
  - **Clinical Studies:** multiple batches; dose response
  - **Bioassay**
  - **Analytical Testing:** chromatography; spectroscopy
  - **Manufacturing Process Control**



**Case study of Fulyzaq  
to illustrate  
the totality of evidence  
approach to an NDA**

## Example: Fulyzaq

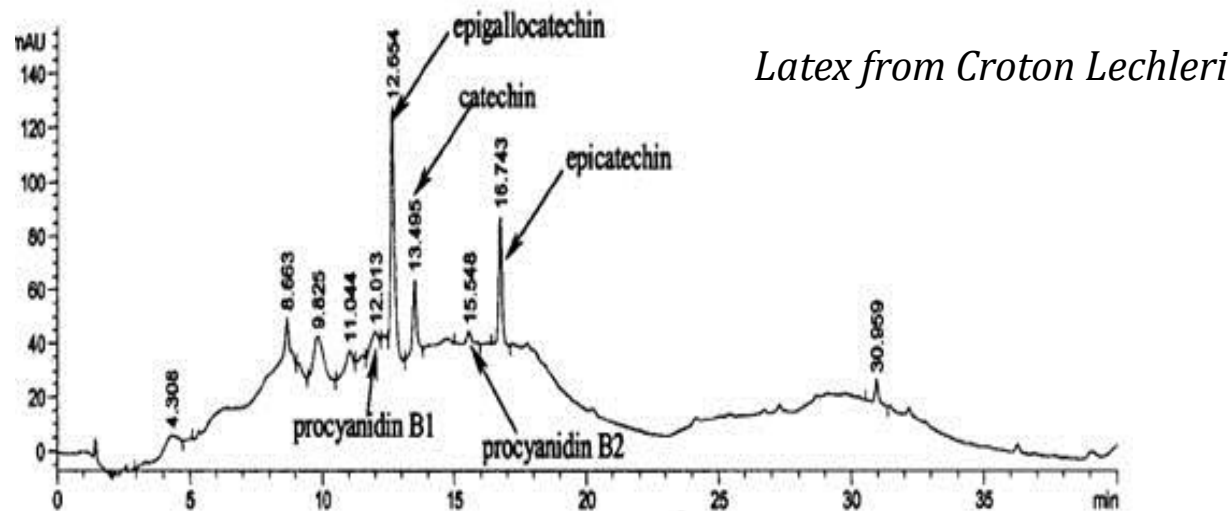
- Delayed-release oral tablet containing 125 mg crofelemer
- Crofelemer, a botanical drug substance derived from the crude plant latex of *Croton lechleri* (*Dragon's Blood*)



- Approved on December 31, 2012
- 1<sup>st</sup> FDA approved drug for symptomatic relief of noninfectious diarrhea in patients with HIV/AIDS on antiretroviral therapy

# Crofelemer Structure

- A oligomeric proanthocyanidin mixture primarily composed of (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin monomer units linked in random sequence



- Multiple analytical methods were used to characterize the structural signatures of crofelemer (e.g., the composition of proanthocyanidin oligomers)
- These analytical methods were ultimately considered insufficient to support the characterization of this complex mixture

# Additional Data to Support Therapeutic Consistency of Fulyzaq

- Botanical raw material control
  - Implementation of Good Agricultural and Collection Practices (GACP)
  - Restriction of harvesting botanical raw material to specific eco-geographic regions (EGRs)
  - **Reduces the variability at the plant and raw material levels**
- Bioassay
  - Developed based on well-known Crofelemer's mechanism of action (i.e., targets and controls dual intestinal chloride channels: cAMP-stimulated cystic fibrosis transmembrane conductance regulator Cl<sup>-</sup> channel and the calcium-activated Cl<sup>-</sup> channel)
  - **Potentially provides more flexibility for the manufacturer to make postapproval changes (e.g., expansion of EGRs to increase and diversify the botanical raw material supply)**

# Additional Data to Support Therapeutic Consistency of Fulyzaq

Dose-response clinical data generated based on multiple batches

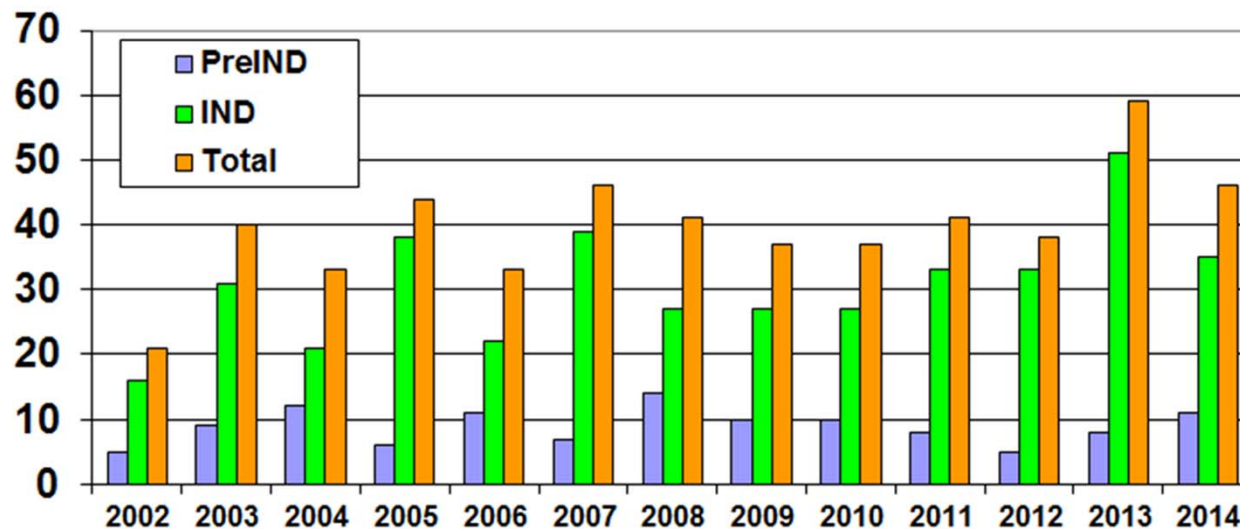
- The drug's effects were not sensitive to the dose in a range of 125 – 500 mg bid
- The estimated drug concentrations in the GI tract after oral dosing of 125 mg bid are several-fold higher than the concentrations used to saturate the targeted chloride ion channels
- Multiple batch data did not reveal noticeable clinical differences among drug product batches manufactured using different drug substance batches
- Natural variations observed in crofelemer were unlikely to have significant impact on the efficacy of Fulyzaq



# Botanical Applications in CDER

Up to 2014

- More than 600 pre-INDs/INDs
- Approx. 1/3 commercial, 2/3 research
- Two NDAs submitted and approved



# Lesson Learned from Botanical NDAs

## New therapies from old medicines

Shaw T Chen, Jinhui Dou, Robert Temple, Rajiv Agarwal, Kuei-Meng Wu & Susan Walker

Although new botanical drugs pose many challenges for both industry and the FDA, approval of the first botanical prescription drug shows they can be successfully met.



Green tea leaves are the source for sin catechins, the active ingredients of Veregen—the first botanical product to be approved as a prescription drug by the FDA.

<http://www.nature.com/nbt/journal/v26/n10/pdf/nbt1008-1077.pdf>

## Evolution of traditional medicines to botanical drugs

**Authors:**  
Sau L. Lee\*,  
Jinhui Dou\*,  
Rajiv Agarwal,  
Robert Temple,  
Julie Beitz,  
Charles Wu,  
Andrew Mulberg,  
Lawrence X. Yu,  
Janet Woodcock

**B**otanicals constitute an important source for new drugs (1, 2). To facilitate botanical drug development, the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) established the Botanical Review Team in 2003 and published its first *Guidance for Industry: Botanical Drug Products* in 2004 (3). This guidance represents FDA's thinking and provides recommendations on quality, nonclinical, clinical, and other unique aspects associated with botanical new drug development through the investigational new drug (IND) and new drug application (NDA) processes. From 2004 to 2013, CDER received over 400 botanical IND applications and pre-IND meeting requests (Table 1). Most of the INDs were allowed to enter phase 2 clinical trials for evaluation of preliminary safety and efficacy of the investigational botanical products in patients. FDA approved the first botanical NDA for Veregen (sin catechins) in 2006 (4, 5) and the second botanical NDA for Fulyzaq (crofelemer) in 2012 (6, 7). These two NDA approvals show that new therapies

generated by  
The degree of  
consistency in  
botanical medicine  
an integrated approach  
through the  
NDAs.

### Veregen

Veregen (sin catechins) is a topical treatment for hemorrhoids (4, 5). It contains the active substance theaflavin-3-gallate extract of green tea (Theaceae). Theaflavin-3-gallate accounts for 95% by weight of the total catechin tea component. Theaflavin-3-gallate is an epigallocatechin gallate (Figure 1A) (6). For FDA approval, theaflavin-3-gallate was established as a botanical drug controlled substance. The treatment

*Science* 2015 Jan 16;347(6219 Suppl.):S32-4  
[http://www.sciencemag.org/site/products/collections/nbooks/TCM\\_Jan\\_16\\_2015\\_high%20res.pdf](http://www.sciencemag.org/site/products/collections/nbooks/TCM_Jan_16_2015_high%20res.pdf)



# Methylsulfonylmethane (MSM)

**Pharmacy Compounding Advisory Committee Meeting**  
**October 27, 2015**

**Anjelina Pokrovnichka, MD (Clin. Reviewer), Medical Officer**  
**Division of Anesthesia, Analgesia, and Addiction Products**



# Methylsulfonylmethane (MSM)

## Review Team

**Anjelina Pokrovnichka, MD (Clin. Reviewer), Medical Officer  
Division of Anesthesia, Analgesia, and Addiction Products**

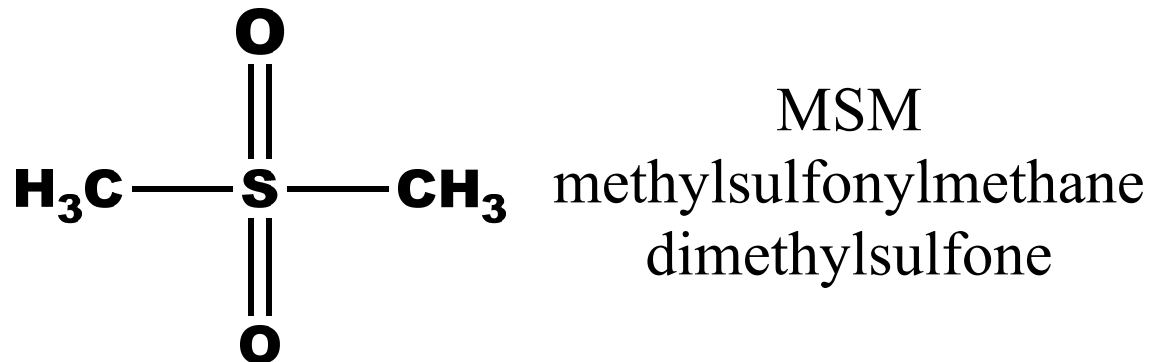
**Norman R. Schmuff, PhD (Quality Reviewer), Associate Director for Science  
Office of Process and Facilities**

**Nikunj Patel, PhD (Nonclin.) Pharmacology/Toxicology Reviewer  
Division of Anesthesia, Analgesia, and Addiction Products**

## MSM Uses

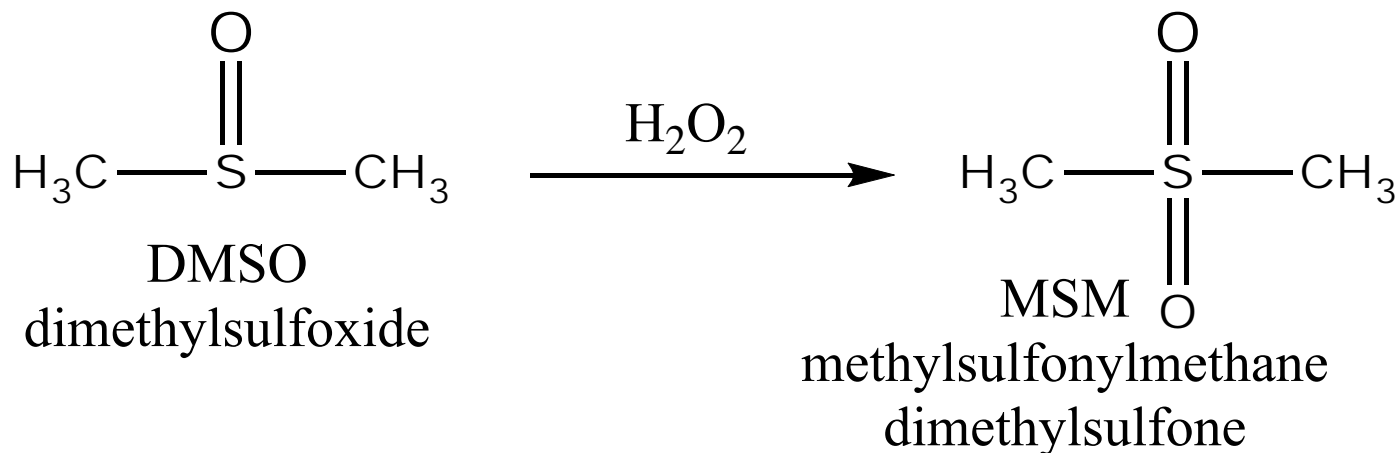
- Most common use: treatment of the pain of osteoarthritis
- Variety of other uses:
  - Musculoskeletal pain
  - Disorders with collagen defects
  - Inflammation
  - Gastrointestinal upset
  - Allergies
  - Boosting the immune system
  - Snoring

# MSM



- White crystalline solid
- Melting point: 109 °C
- Stable in all dosage forms
- Aqueous solubility: 150 mg/mL

## MSM Synthesis



- Possible impurities:
  - DMSO
  - H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide)

Conclusion: MSM is a well-characterized small molecule, with good stability properties.

# MSM

## Nonclinical Assessment-1

- Pharmacology
  - MSM has been reported to possess anti-oxidant, anti-apoptotic, and anti-inflammatory properties. However, no mechanism of action has been characterized to date.
- Safety Pharmacology
  - No information was available regarding the impact of MSM on the central nervous, cardiovascular, or respiratory systems.
- Acute Toxicity
  - Oral LD<sub>50</sub> > 2 g/kg in mice, rats, and dogs.
- Repeat-dose Toxicity
  - No adverse toxicities identified in rats administered 1.5 g/kg MSM orally once daily for 90 days.
  - No observed adverse effect level > 1.5 g/kg/day, corresponding to a human equivalent dose of 14.5 g/day



# MSM

## Nonclinical Assessment-2

- Mutagenicity
  - MSM was negative for mutagenic potential in a genetic toxicology battery consisting of in vitro (bacterial reverse mutation and chromosomal aberration) and in vivo (mouse micronucleus) assays.
- Developmental and reproductive toxicity
  - No maternal or fetal toxicity was observed in a rat developmental toxicity study in which doses of up to 1 g/kg/day (equivalent to a human dose of 9.6 g) were administered to dams during organogenesis (Gestational Days 6 - 20).

# MSM

## Nonclinical Assessment-3

- Carcinogenicity
  - 2 studies have suggested that MSM can delay the onset of chemically induced tumors in rats.
  - Several in vitro and in vivo studies have suggested that MSM is cytotoxic to cancer cell lines.
- Toxicokinetics
  - Following oral administration in rats, MSM was detectable in plasma within 15 minutes and remained detectable in plasma and tissues for up to 48 hours. High levels were found in blood, kidneys, testes, and eyes, and significant levels were found in brain. The majority of MSM was excreted by 48 hours post dose, via the urine.

# MSM

## Nonclinical Assessment-4

- Nonclinical Conclusions
  - No evidence of adverse effects based on limited data available
- BUT, there are data missing
  - Chronic toxicology in any species
  - Fertility and early embryonic development
  - Embryo-fetal development in a second species
  - Pre- and postnatal development
  - Carcinogenicity assessment in two species

# MSM

## Human Safety Data – Clinical Trials

### Clinical trials for use in osteoarthritis

- Usha P, Naidu M: Randomized, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clin Drug Invest* 2004, 24:353-263.
- Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF: Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial. *Osteoarthritis Cartilage* 2006, 14:286-294.
- Brien S, Prescott P, Lewith G: Meta-analysis of related nutritional supplements dimethyl sulfoxide and methylsulfonylmethane in the treatment of osteoarthritis of the knee. *Evid Based Complement Alternative Medicine*, 2011: 2011:528403.

# MSM

## Human Safety Data - Clinical Trials

### Clinical trials for use in osteoarthritis (*con't*)

- Brien S, Prescott P, Bashir N, Lewith H, Lewith G: Systemic review of nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 2008, 16:1277-1288.
- Debbi EM, Agar G, Fichman G, Ziv YB, Kardosh R, Halperin N, et al. Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study. *BMC complementary and alternative medicine*. 2011;11:50. Epub 2011/06/29. doi: 10.1186/1472-6882-11-50.
- Ameye LG, Chee WS. Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. *Arthritis research & therapy*. 2006;8(4):R127. Epub 2006/07/25. doi: 10.1186/ar2016

## MSM

# Human Safety Data - Reported Adverse Events in Osteoarthritis Clinical Trials

- Doses investigated
  - 500 mg and 1.125 g three times daily orally
  - Up to 3 g twice daily orally
- No serious adverse events (AEs) reported
- Common AEs: Gastrointestinal (GI) upset, fatigue, insomnia, and headache
- Other AEs
- Limitations
  - Small trials with limited safety data and no long-term safety assessments beyond 12 weeks
  - Poor quality of adverse event reporting

## MSM

# Human Safety Data – FAERS (FDA Adverse Event Reporting System) Adverse Reactions

- Most commonly reported: fatigue, nausea, cough, drug ineffective, drug interaction, dyspnea, hematoma, headache, increased international normalized ratio (INR), product quality issue, and somnolence
- Four cases of bleeding or INR increase
- FAERS limitations
  - FDA does not receive all AE reports that may occur with a product
  - FDA does not have sales data to estimate a denominator and calculate an AE rate

# MSM: Efficacy

- Randomized, controlled osteoarthritis clinical trials: Usha et al., Kim et al., and Debbi et al.
- Meta-analysis: Ameye et al. and Brien et al.
- Assessments of pain based on validated instruments:
  - Western Ontario and McMaster Universities Arthritis Index (WOMAC), Visual Analog Scale (VAS) pain, and Likert pain scale
- Findings
  - Small improvements in pain
  - Some failed statistical tests
  - The changes in pain and function not considered clinically significant improvements according to the Outcome Measures in Rheumatoid Arthritis Clinical trials (OMERACT) and Osteoarthritis Research Society International (OARSI) criteria



## MSM: Efficacy, *cont.*

- Limitations
  - Small trials, 77 patients total treated with MSM alone
  - MSM dosage varied: from 500 mg TID to 3 g BID for 12 weeks
  - Not clear if the effect of rescue medication (medications taken if pain not treated effectively by MSM) on efficacy outcome was analyzed
  - Concerns about the statistical analyses used in the studies

# MSM

## Historical Use in Compounding

- Information for the historical use of MSM in pharmacy compounding was not found.

## Conclusions

- Use of MSM reported in many countries
- Well characterized physically and chemically
- Non-clinical safety profile not adequately characterized
- Adverse events in humans mostly not serious
- Events of concern
  - Possible interaction with anticoagulants and risk of bleeding
  - Increase in blood pressure
- Limited evidence for clinically significant reduction of joint pain associated with osteoarthritis
- Existence of approved alternative treatments that are safe and effective (i.e., acetaminophen and non-steroidal anti-inflammatory drugs such as ibuprofen)

## Recommendation

Because of gaps in both nonclinical and clinical information on MSM, limited evidence of efficacy, the availability of approved alternatives, and the potential risks identified of interaction with anticoagulants and subsequent bleeding, and increased blood pressure, we recommend that MSM **not be included** in the list of bulk drug substances that can be used for compounding under Section 503A of the FD&C Act.



# Curcumin

## Pharmacy Compounding Advisory Committee Meeting October 27, 2015

**Sandra Casak, MD, Medical Officer, DOP2/OHOP**



# Curcumin

## Review Team

**Rajiv Agarwal, PhD, CMC Reviewer, DNDPI**

**Ramesh Sood, PhD, Acting Senior Scientific Advisor, ONDP**

**Shawna Weis, PhD, Pharmacologist, DHOT/OHOP**

**Whitney Helms, PhD, Supervisory Pharmacologist, DHOT/OHOP**

**John Leighton, PhD, DABT, Acting Division Director, DHOT/OHOP**

**Stacy Shord, Pharm D, Clinical Pharmacologist, DCPV**

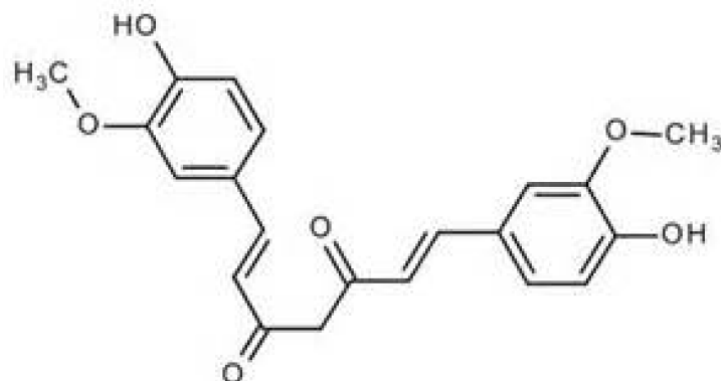
**Hong Zhao, PhD, Clinical Pharmacology Team Leader, DCPV**

**Sandra Casak, MD, Medical Officer, DOP2/OHOP**

**Steven Lemery, MD, MHS, Clinical Team Leader, DOP2/OHOP**

**Patricia Keegan, MD, Division Director, DOP2/OHOP**

# Curcumin



- **Molecular Formula:** C<sub>21</sub>H<sub>20</sub>O<sub>6</sub>
- **Molecular weight:** 368.37
- **Chemical name:** Diferuloylmethane (Curcumin or Curcumin I)
- **Common name:** Turmeric yellow or Natural Yellow 3
- Occurs naturally along with Curcumin II and Curcumin III (extraction produces C3 complex that includes Curcumin I, II, and III, and the percentage of each varies)

# Curcumin

## **Impurities identified in curcumin preparations**

Heavy metals

Pesticides

Aflatoxins

Residual solvents

## **Degradation products (in solution)**

Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexanal

Vanillin

Vanillic acid

Ferulic acid

Feruloyl methane



# Curcumin

## Probable routes of API synthesis

- Solvent extraction from Turmeric roots (*Curcuma longa*)

## Stability

- Stable in the solid state under ambient conditions
- Can undergo photodegradation
- Unstable in solution at neutral to basic pH
- Due to instability, avoid preparations that include water

# Curcumin

## Nonclinical Assessment - 1

**Proposed pharmacology:** Antioxidant

**Safety Pharmacology:** No information available

**Acute Toxicity:**

- Low, likely due to poor oral bioavailability
- The LD<sub>50</sub> is > 2 g/kg in the rat

**Repeat-dose Toxicity:**

- Hyperplasia of cecum in rat at doses of 2.8 g/kg in a 13-week study
- Hyperplasia/inflammation/ulceration of forestomach in rats at doses of >2 g/kg in carcinogenicity study

# Curcumin

## Nonclinical Assessment - 2

### Carcinogenicity (National Toxicology Program)

- **Rat:** equivocal evidence of carcinogenic activity in rats
  - clitoral gland adenoma at doses of  $>2$  g/kg/day
- **Mouse:** equivocal evidence of carcinogenic activity in B6C3F1 mice
  - non-dose-related hepatocellular adenoma and carcinomas of the small intestine

# Curcumin: Proposed Indications

- **Familial adenopolyposis (FAP)**
  - Colorectal cancer occurs in nearly 100 percent of individuals if untreated
  - Average age of 45 years at cancer diagnosis
  - Only effective treatment is surgery
  - Chemopreventive strategies only in conjunction with strict endoscopic surveillance in clinical trials; not currently recommended
- **Oral leukoplakia**
  - Hyperplasia of the squamous epithelium that can be precancerous (1-20% will progress to carcinoma within 10 years)
  - Lesions with high degree of dysplasia require ablation
- **Gastric metaplasia**
  - Dysplastic condition associated with increased risk of gastric cancer

# Curcumin: Clinical Efficacy Data

- Multiple studies in many different diseases including different types of cancer.
- Effects on biomarkers observed
- No evidence of efficacy for listed conditions

# Limitations of Curcumin Studies

- Poor bioavailability of curcumin
- Limited exposure (up to 12 weeks)
- Different doses studied
- Different products used
- Studies small and inconclusive

# Safety Data from Clinical Trials

- Mostly well tolerated for short duration
- Reported adverse events include nausea, diarrhea, dyspepsia
- Safety of long-term use cannot be ascertained
  - Poor bioavailability
  - Lack of exposure-response for toxicity
  - Lack of uniformity of products and doses used
  - Limited well-designed trials
  - Potential for prolonged exposure to impurities
  - Potential for drug-drug interactions
  - Limited and inconsistent reporting of adverse events

## Curcumin in FAP

- Cruz Correa M., 2006. Five patients with prior colectomy received combination therapy of curcumin and quercetin for 6 months. Number and size of polyps reported to have decreased.
- Weaknesses of the study
  - Unblinded, small
  - No isolation of curcumin's treatment effect
  - Lack of reporting of concomitant NSAIDS use
  - Assessments performed by a single observer



## Curcumin in Oral Leukoplakia

- Cheng A., 2001. Chemoprevention study in patients at high risk of cancer (CIN, oral leukoplakia).
  - Seven patients with oral leukoplakia treated with curcumin: Although two patients showed signs of improvement, *one developed frank malignancy.*

## Curcumin in Gastric Metaplasia

- No dedicated reports in the literature.
- Cheng A., 2001. *One of six patients developed gastric cancer.*

# Curcumin: Conclusions

- Long-term safety not established
- Even for short-term use, poor bioavailability, different formulations, and doses used in small, uncontrolled clinical studies in multiple conditions prevent us from concluding that curcumin use is safe
- For all nominated conditions, no evidence of efficacy; furthermore, uncontrolled use of curcumin may increase the risk of malignancy
- Lack of information about historical use in compounding
- Use of curcumin may delay effective treatment of the serious conditions for which curcumin was nominated

## Curcumin: Recommendation

We recommend that curcumin **not** be placed on the list of bulk substances that can be used to compound under section 503A of the FD&C Act.



# Germanium Sesquioxide

**Pharmacy Compounding Advisory Committee Meeting**  
**October 27, 2015**

**Sanjeeve Balasubramaniam, MD, MPH (Clin. Reviewer), Medical  
Officer, Division of Oncology Products 1, OHOP**



# Germanium Sesquioxide

## Review Team

**Sanjeeve Balasubramaniam, MD, MPH (Clin. Reviewer), Medical Officer, Division of Oncology Products 1, OHOP**

**Wei Chen, PhD (Pharm/Tox Reviewer), Pharmacologist/Toxicologist, Division of Hematology Oncology Toxicology, OHOP**

**Ximing Liu, PhD, (Chem. Reviewer), Fellow, Office of Product Quality**

**Amy McKee, MD, Clinical Team Leader, Division of Oncology Products 1, Office of Hematology and Oncology Products**

**Geoffrey Kim, MD, Director, Division of Oncology Products 1, Office of Hematology and Oncology Products**

**Todd Palmby, PhD, Supervisory Pharmacologist/Toxicologist Reviewer, Division of Hematology, Oncology, Toxicology, Office of Hematology and Oncology Products**

**Norman Schmuff, PhD, Associate Director for Product Quality, Office of Pharmaceutical Quality**

# Germanium Sesquioxide: Nomination

- For “Treatment of patients with cancer and chronic illnesses”
- Germanium sesquioxide (GS) as an injection with strength of 100mg/mL administered via slow intravenous infusion

# Germanium Sesquioxide

- Sometimes seen in dietary supplements
  - Supplements containing GS are considered **adulterated** due to safety concerns and **cannot be sold legally**
- There is an active import alert for all germanium compounds, except those used for semiconductors
  - FDA Import Alert #54-07
    - “nonessential trace element that has caused nephrotoxicity (kidney injury) and death when used chronically by humans, even at recommended levels of use”
  - Toxic germanium compounds involved in synthesis
  - Contaminates germanium sesquioxide

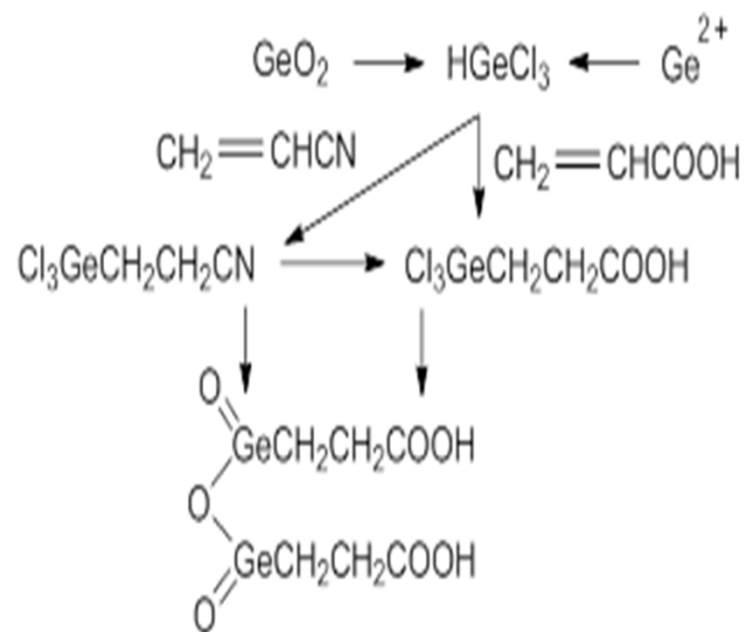
# Chemistry

- Synonyms: Propagermanium, bis(2-carboxyethylgermanium) sesquioxide, 2-carboxyethylgermanium sesquioxide, carboxyethylgermanium sesquioxide, 2-carboxyethylgermasesquioxane, proxigermanium, repagermanium, organic germanium, Ge-132, and SK-818
- Stability: Stable when stored in a tightly closed container, unstable when exposed to high humidity



# Chemistry: Synthesis

- Originally synthesized by Mironov and coworkers in Russia
  - Acrylonitrile and trichlorogermane starting materials (Tsutsui, 1976; Asai, 1974; Kaplan, 2004)
  - Method cited in Merck Index; remains most probable synthetic route for producing GS
- Similar methods developed using acrylonitrile or acrylic acid
  - Key reaction intermediate trichlorogermane synthesized using  $\text{GeO}_2$ ,  $\text{Ge}(\text{OH})_2$ ,  $\text{GeCl}_2$ ,  $\text{GeS}$  (most probably  $\text{GeO}_2$ ) as starting materials (Chang, 1985; Arnold, 1996; Sun, 1995; Zhang, 2000)



# Impurities

- Starting materials
  - **Inorganic germanium salts** (Kaplan, 2004): contamination of GS with dangerous levels of inorganic germanium salts (e.g.,  $\text{GeO}_2$ ), which accumulate in the body and cause toxicity (Tao, 1997; Luck, 1999; Sanai, 1991).
  - **Acrylonitrile and acrylic acid**: excess acrylonitrile is converted to acrylamide during the hydrolysis step of synthesis. All contain structural alerts for genotoxicity.
- Reaction intermediate **trichlorogermane**: complex structures, unknown safety

## Chemistry, Conclusion

- From physicochemical point of view, germanium sesquioxide is well characterized.
- Due to the demonstrated toxicity of likely impurities, germanium sesquioxide is not recommended for inclusion list of bulk drug substances that may be used in compounding under section 503A of the FD&C Act.

# Nonclinical Assessment

- Hypothetical mechanism of action
  - Induced IFN-gamma, enhanced NK-cell activity in vitro and in vivo; inhibited tumor and metastasis growth in animal models (Kaplan, 2004). Animal models uncommonly accurately predict efficacy in humans.
- Safety pharmacology
  - IP administration of water-soluble GS
    - Dose-related reduction in mean arterial pressure or heart rate in anesthetized rats (Ho, 1990)
  - IP administration (250 mg/kg) did not show any antinociceptive action by assessing the tail-flick test and the hot-plate test (Hachisu, 1983)

## Nonclinical Assessment, *cont.*

- Acute toxicity: Median Lethal Dose (LD50)
  - Acute IP administration of GS in mice 1250 mg/kg
    - Behavioral changes, including somnolence, and muscle contraction or spasticity, were the major adverse effects.
  - Acute IV administration in mice was 233mg/kg
  - Acute IP administration in rats was 1700mg/kg
  - Acute IV administration in rats was greater than 200 mg/kg

## Nonclinical Assessment, *cont.*

### Repeat Dose Toxicity

- Male and female rats orally administered 1 mg/kg/day 28 days or 6 months
  - No particular clinical signs, no behavior changes observed
  - Small decrease in body weight observed in male rats after oral administration of GS at 1 mg/day for 6 months
  - Slight decrease in erythropoiesis and a general stimulation of cellular metabolism observed after 28 days
  - Moderate renal deficiency (tubular disease with presence of cylinders, swelling of tubular cells) observed after 6 months (Anger, 1991)

## Nonclinical Assessment, *cont.*

- Mutagenicity: No mutagenic activity in in vitro reverse mutation assay in bacterial cells (Gerber, 1997)
- Developmental and reproductive toxicity: No study reports identified; the organic compound dimethyl germanium oxide reported to be teratogenic in chick embryos
- Carcinogenicity: Germanium compounds not carcinogenic in mice or rats (Gerber, 1997)
- Toxicokinetics: No information available

## Nonclinical Assessment: Conclusions

- Germanium sesquioxide does not appear to be mutagenic or carcinogenic. However, there are inadequate nonclinical data to otherwise characterize the safety profile of GS at high doses.
- The nephrotoxicity of inorganic forms of germanium is well established. The potential nephrotoxicity from organic germanium compounds cannot be excluded due to lack of conclusive findings.
- Developmental and reproductive toxicity were observed in the studies with other germanium compounds



# Clinical Assessment: Safety

- Clinical trials available for evaluation, including citations provided in the nomination, are for another form of organic germanium: spirogermanium.
  - Significant, life-threatening safety concerns arose during clinical trials with this agent in the 1980s (Vogelzang, 1985; Ettinger, 1989; Ettinger, 1990).
- No clinical trials assessing the safety of **germanium sesquioxide**
- No pharmacokinetic data available for evaluation

## Clinical: Safety Conclusions

- The limited information available about the safety of germanium sesquioxide gives rise to significant concern about its use in compounding.
- It seems likely that the substance could be contaminated with highly toxic inorganic forms of germanium salts.
- Prolonged intake of germanium products has been associated with at least 31 cases of renal failure, some of which led to death.

## Clinical: Efficacy

- Limited clinical information available for germanium sesquioxide
  - One case report (Mainwaring, 2000)
    - Patient with spindle-cell carcinoma of the lung, immediately following treatment with chemotherapy and surgery, self-administered 7.2 g/d oral germanium sesquioxide and purportedly had a complete response.
  - A trial in *Clinicaltrials.gov* opened in 2005 to assess the efficacy of oral organic germanium on cancer fatigue, with no results reported; attempts to contact the sponsor unanswered
- The nomination of the product is for a serious and life-threatening disease (cancer)

## Clinical Efficacy: Conclusions

- There is no evidence available in the literature that would indicate that germanium sesquioxide is effective for the treatment of cancer.
- There are numerous FDA-approved products that have been demonstrated to be effective in the treatment of cancer.

## General Conclusions

- We have evaluated germanium sesquioxide for use in compounding based on its physicochemical characteristics, safety, effectiveness, and evidence of historical use in compounding.
- Although it is physically and chemically well characterized, it can include impurities with significant toxicities. The nephrotoxicity of inorganic forms of germanium (e.g., germanium dioxide or germanium citrate lactate) is well established.
- Clinical evidence for the efficacy of germanium sesquioxide in oncology is lacking.

## Recommendation

Based on our evaluation of the four criteria identified above, we *do not recommend* that germanium sesquioxide be included on the list of bulk drug substances that can be used in compounding in accordance with section 503A of the FD&C Act.



# Rubidium Chloride

**Pharmacy Compounding Advisory Committee Meeting  
October 27, 2015**

**Sanjeeve Balasubramaniam, MD, MPH (Clin. Reviewer), Medical Officer,  
Division of Oncology Products 1, OHOP**



# Rubidium Chloride

## Review Team

**Sanjeeve Balasubramaniam, MD, MPH (Clin. Reviewer), Medical Officer, Division of Oncology Products 1, OHOP**

**Wei Chen, PhD (Pharm/Tox Reviewer), Pharmacologist/Toxicologist, Division of Hematology Oncology Toxicology, OHOP**

**Ximing Liu, PhD (Chem. Reviewer), Fellow, Office of Product Quality**

**Amy McKee, MD, Clinical Team Leader, Division of Oncology Products 1, Office of Hematology and Oncology Products**

**Geoffrey Kim, MD, Director, Division of Oncology Products 1, Office of Hematology and Oncology Products,**

**Todd Palmby, PhD, Supervisory Pharmacologist/Toxicologist Reviewer, Division of Hematology, Oncology, Toxicology, Office of Hematology and Oncology Products**

**Norman Schmuff, PhD, Associate Director for Product Quality, Office of Pharmaceutical Quality**



# Rubidium Chloride: Nomination

- For the treatment of numerous types of cancer
- As an injection from strengths of 0.54 mcg/mL to 282 mcg/mL to be administered by slow intravenous infusion

# Historical Description of Rubidium Chloride in Cancer Treatment

- A. Keith Brewer, a physicist, determined that the Hopi Indians of Arizona have a low rate of cancer (1 in 1000 vs 1 in 4 Americans).
- RbCl is found in the soil in higher concentrations around Hopi reservations; Brewer asserted that this led to prevention of cancer.
- Proposed mechanism of action is that rubidium cations compete with potassium in gated channels, causing alkalinization of tumor cells and their microenvironment.
- Brewer performed experiments with patients in the 1960s-70s, occasionally with cesium instead of rubidium, and occasionally in combination with laetrile, in what he called “high pH therapy” (Brewer, 1984).

## Rubidium “High pH Therapy”

Brewer reported

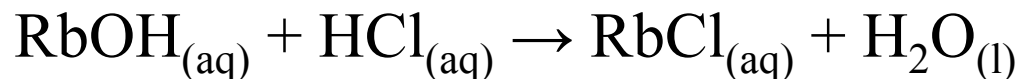
“In addition to the loss of pains, the physical results are a rapid shrinkage of the tumor masses. The material comprising the tumors is secreted as uric acid in the urine, the uric acid content of the urine increases many fold. About 50% of the patients were pronounced terminal, and were not able to work. Of these, a majority have gone back to work.”

## Rubidium Chloride: Uses

- Current documented use of RbCl
  - Limited to  $^{82}\text{Rb}$ -based radionuclide imaging for cardiac perfusion studies
  - Based on radioactive isotope of rubidium with a half-life of 75 seconds that releases positrons, and is used in cardiac positron emission tomography (Cardiogen-82)
- No other current uses of RbCl were found in the medical literature, including international pharmacopoeias
- The nominated compound is intended for application in a serious and life-threatening disease (cancer)

# Chemistry

- RbCl is physicochemically well characterized.
- Synthesis:



- Per the Acros Organics Material Safety Data Sheet (MSDS)
  - RbCl is stable under normal temperatures and pressures.
  - Rb<sub>2</sub>O is hygroscopic and reactive and can react exothermically with water, forming stable RbOH. Likely impurity in RbCl product is RbOH when Rb<sub>2</sub>O or/and RbOH used as starting materials.

# Nonclinical Assessment

- Rubidium compounds are only slightly toxic on an acute toxicological basis, but pose an acute health hazard when ingested in large quantities (Johnson, 1975).
- According to the U.S. National Library of Medicine's (NLM) Toxicology Data Network ([TOXNET](#))
  - RbOH is designated as more toxic than other salts of this metal; designated as a pneumotoxin, hepatotoxin, and dermatotoxin (Johnson, 1975).
  - Minimum toxic concentration: 5.75 mg RbOH/m<sup>3</sup>; recommended maximum permissible concentration for occupational exposure is 0.5 mg RbOH/m<sup>3</sup> (Hamidulina, 1987).

## Nonclinical Assessment

- Rubidium is an alkali metal belonging to the same periodic series as sodium, potassium, lithium, and cesium.
- Brewer's own studies: in mouse tumor models, shrinkage of tumor masses shown after 2 weeks in mice fed a diet containing cesium and rubidium (1.11 mg/day) (Brewer, 1984; Brewer, 1979).
  - **These studies have not been replicated using RbCl in relevant models.**

## Nonclinical Assessment, *cont.*

- RbCl decreases locomotion and rearing in the exploratory box test.
  - Also decreased locomotion in the open field test (Syme GJ, 1979)
- Long-term treatment of rats
  - Behavioral hypo-reactivity and decreased dopamine output in the nucleus accumbens at the lowest dose tested of 0.008 mEq/kg (Gambarana, 1999)
- Acute toxicity: mouse LD50 233 mg/kg (NYZ, 1960)
- Repeat-dose toxicity:
  - Diets containing 0.02% rubidium or less not toxic to rats
  - Diets containing 0.1% rubidium or more were toxic
    - Worsening/decreased growth, general condition, reproductive performance, and survival time



## Nonclinical Assessment, *cont.*

- No mutagenicity information available
- No long-term reproductive and developmental toxicity studies available
- No carcinogenicity information available
- No toxicokinetic studies identified. It is reported that plasma rubidium rapidly reaches a steady-state distribution with the extracellular space.

**Conclusions:** Administration of rubidium to rats affected their growth and survival times and resulted in behavioral changes. Available nonclinical data are inadequate to determine whether rubidium would be safe to use in compounding.

# Rubidium Chloride: Clinical Studies

- Reported adverse reactions:
  - No data with which to assess the safety of RbCl for the treatment of cancer.
  - In a case series reported by Brewer (1984), patients exposed to experiments with “high-pH therapy” using **either cesium or rubidium** experienced nausea and diarrhea.
  - Further details on these two listed toxicities, including severity (i.e., grade) and duration, **not** reported.
- OSE search of the FAERS database did not return any results for RbCl except when used as an imaging agent for positron imaging tomography.

## Rubidium Chloride: Clinical Studies, *cont.*

- Clinical trials assessing safety
  - **No other modern clinical trials** assessing the safety of RbCl for the treatment of cancer.
  - Only trial reported in the medical literature, from 1984 (Brewer, 1984), presented aggregated data on 30 cancer patients.
  - No supporting clinical trials published in peer-reviewed journals were submitted in the nomination for the treatment of cancer
- There are no pharmacokinetic data from which to draw conclusions.

# Rubidium Chloride: Efficacy in Cancer Treatment

## Conclusions

- Although RbCl was first discussed by Brewer in the 1960s, insufficient data are available to assess the historical use of RuCl in compounding. Brewer's claims, however, were not supported by any further evidence.
- There are insufficient data to attest to the safety or efficacy of RbCl in the treatment of cancer.
- Numerous FDA-approved products have been demonstrated to be effective in the treatment of cancer.

## Recommendation

Because of insufficient data to assess its historical use in compounding, the lack of data on safety or efficacy, and because of the availability of approved medications to treat cancer, we recommend that rubidium chloride *not* be placed on the list of bulk substances that can be used for compounding under Section 503A of the FD&C Act.



# Deoxy-D-Glucose for the Treatment of Cancer

**Pharmacy Compounding Advisory Committee Meeting  
October 27, 2015**

**Sanjeeve Balasubramaniam, MD, MPH (Clin. Reviewer), Medical  
Officer, Division of Oncology Products 1, OHOP**



# Deoxy-D-Glucose for the Treatment of Cancer

## Review Team

**Sanjeeve Balasubramaniam, MD, MPH (Clin. Reviewer), Medical Officer, Division of Oncology Products 1, OHOP**

**Wei Chen, PhD (Pharm/Tox Reviewer), Pharmacologist/Toxicologist, Division of Hematology Oncology Toxicology, OHOP**

**Ximing Liu, PhD, (Chem. Reviewer), Fellow, Office of Product Quality**

**Amy McKee, MD, Clinical Team Leader, Division of Oncology Products 1, Office of Hematology and Oncology Products**

**Geoffrey Kim, MD, Director, Division of Oncology Products 1, Office of Hematology and Oncology Products**

**Todd Palmby, PhD, Supervisory Pharmacologist/Toxicologist Reviewer, Division of Hematology, Oncology, Toxicology, Office of Hematology and Oncology Products**

**Norman Schmuff, PhD, Associate Director for Product Quality, Office of Pharmaceutical Quality**

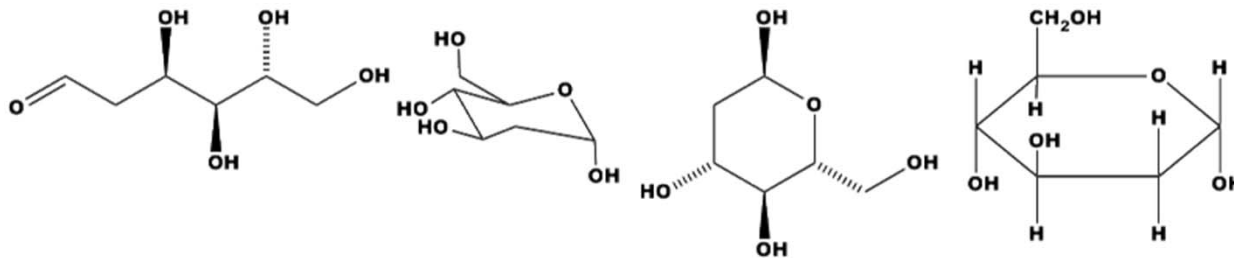
## Deoxy-D-Glucose: Uses Evaluated

- Nominated for use as *chemotherapy*
- Also nominated for treatment of viral infections such as HSV (discussed in a separate presentation)



## Deoxy-D-Glucose: Chemistry

- Rare naturally occurring monosaccharide
- Diverse representation of its forms:



- Very soluble in water
- Synthesized from other monosaccharides

## Chemistry, *cont.*

- Toxicity of likely impurities
  - D-Glucal and 3,4,6-tri-O-acetyl-D-glucal
    - **Reactive** double bond: may react with normal cellular molecules
  - D-Glucal
    - Replaces glucose-1-phosphate in phosphorylase-catalyzed glucosyl transfer (Klein, 1982).
- Chemistry conclusions
  - 2-DG is physiochemically well characterized by spectroscopic and physicochemical means.

# Nonclinical Assessment

- 2-DG competitively inhibits glucose transport
  - Shares the same glucose transporters and enzymes in all human cells
  - Forms 2-DG-6-phosphate, which is not metabolized further
- 2-DG-6-phosphate inhibits phosphohexoisomerase and G-6-PD
  - Reduces output from glycolysis (ATP) and pentose phosphate pathway (NAPDH) in all human cells
  - In other words, 2-DG blocks energy production from glucose in human cells

## Nonclinical: Hypothesis re: Mechanism of Action

- Normal human cells and cancer cells use glucose to generate metabolic energy (ATP) and as building blocks to sustain growth.
  - 2-DG purportedly depletes cells of energy by inhibiting glucose metabolism in vitro
  - In vitro and in vivo: inhibited aerobic glycolysis in cancer cells, decreased cell proliferation, and increased cell apoptosis (Zhang, 2014)
  - Hypothesis: This can be used to treat cancer; however, normal cells work the same way, and undergo the same injury.
    - Furthermore, cancer cells are now known to be more adaptable than this hypothesis would suppose.

## Nonclinical Assessment: Safety Pharmacology

- Cardiovascular and respiratory effects
  - IV 2-DG (250 mg/kg, 500 mg/kg, and 1000 mg/kg) in anaesthetized rats: decrease in mean arterial blood pressure (Vijayaraghavan, 2006)
- Neurologic effects
  - IP 2-DG in rats at doses up to 1000 mg/kg/day x 14 days: no apparent detrimental effect on spatial learning and memory as assessed by the water maze.
  - In the open field experiments, reduced exploratory activity in a dose-dependent manner, with the effect most marked at the 250 mg/kg dose (Ockuly, 2012).

## Nonclinical Assessment: Safety Pharmacology, *cont.*

- Acute toxicity
  - LD50: Median lethal dose
    - Oral: >8000 mg/kg in mice and rats
    - IV: 8000 mg/kg in mice (Vijayaraghavan, 2006)
- Repeat dose toxicity
  - Dietary supplementation
    - Physiological changes in rats: body weight and food intake declined after 50 weeks in rats on the diets containing 0.4% 2-DG (0.2 g/kg).
    - Cardiotoxic effects in two rat strains, increased mortality in F344 rats, median survival decreased by 45% (Minor, 2010)

## Nonclinical Assessment: Safety Pharmacology, *cont.*

- Mutagenicity
  - No information available
- Developmental and reproductive toxicity
  - IP injections of 2-DG significantly reduced sperm counts in mice after 3-7 days
  - 120mg/day fed to rats from gestational day 9-20 (Demeyer, 1961, cited in Shepard, 1980)
    - Resorption incidence was 69%
    - Surviving fetuses were all malformed
- Carcinogenicity
  - Pheochromocytoma (both benign and malignant tumors of the adrenal gland): 40% in rats given diet with 0.2% or 0.4% 2-DG, vs. 14% in untreated controls.

## Nonclinical Assessment: Safety Pharmacology, *cont.*

- Toxicokinetics
  - No studies reported

### Conclusions

- Dietary supplementation with 2-DG showed cardiac toxicity and decreased median survival in rats.
- 2-DG caused developmental and reproductive toxicities and carcinogenicity in rats.
- The toxicity profile, especially chronic oral exposure, of 2-DG in animal studies weighs against its inclusion on the 503A Bulk Substances list.



# Clinical Assessment: Safety

## Reported adverse reactions

- Flushing, diaphoresis, headache, somnolence, tachycardia, hypoglycemia, reactions similar to hypoglycemia, consistent with one known mechanism of action: inhibition of glycolysis (Landau, 1958)
- Hypoglycemic effect routinely dose-limiting in clinical experience (Singh, 2005; Dwaraknath, 2009)
- OSE search of the FAERS database: no results for 2-deoxy-D-glucose

## Clinical Assessment: Safety, *cont.*

### Clinical trials assessing safety

- A phase 1, dose-escalation trial with 2-DG alone and in combination with docetaxel for advanced solid tumors using an oral formulation at three different dosing schedules (Raez, 2012): adverse reactions described as mild, transient, consistent with severe hypoglycemia.
- Toxicities precluded dose escalation beyond 63 mg/kg when given with docetaxel; this dose not considered to be efficacious

## Clinical Assessment: Safety, *cont.*

- Numerous anticancer agents have been granted marketing approval by FDA after demonstration of safety and efficacy in well-controlled trials.

### Conclusions

- Based on two trials, use of 2-DG for the treatment of cancer appears to be beyond the reach of tolerable dosing in both intravenous and oral dosing regimens.
- The high doses required for single-agent use, based on limited clinical evidence, have led to unacceptable toxicity.

# Clinical Assessment

- Historical use
  - Based on the information available, it appears that the agent has been intermittently in use since the 1950s.
- Medical conditions treated
  - Two clinical trials have been reported for use of 2-DG as a single agent or in combination with chemotherapy for the treatment of cancer. In both cases, there were no tumor responses.
  - It has also been used in anti-viral treatments, especially HSV

# Clinical Assessment: Efficacy

## Reports of trials

- Landau, 1958: IV in 8 patients with cancer: no responses but mild, transient toxicities consistent with hypoglycemia.
- Raez, 2012: limitations of tolerability of oral regimens of 2-DG precluded achieving pharmacodynamically meaningful circulating drug levels
- Dwaraknath, 2009: combined 2-DG with XRT for the treatment of glioblastoma; claimed “increased survival” compared to historical controls—but in the publication, historical controls appear to have had better survival. Details of trial conduct were not publicly available.

## Clinical Assessment: Efficacy, *cont.*

- This compound is intended for the treatment of cancer, a serious and life-threatening disease. Numerous anticancer agents have been granted marketing approval by FDA after demonstration of efficacy in well-controlled trials.

### **Conclusion**

Based on the available data, 2-DG does not appear to be effective for the treatment of cancer.

## General Conclusions

- There are insufficient data to attest to the safety or efficacy of 2-DG in the treatment of cancer.
- In reported controlled trials, toxicity was reached before clinical efficacy.
- A number of safe and effective FDA-approved agents are available for the treatment of cancer.
- The possible uses for 2-DG in the oncology setting, which only includes life-threatening illnesses, are not advisable given the availability of approved products for oncology indications that have been demonstrated to be safe and effective in well-controlled clinical trials.
- Further clinical investigation with 2-DG, if undertaken, should be monitored through the IND process.
- There is insufficient information on the extent of use of 2DG in compounding to evaluate the significance of its historical use



## Recommendation

**We do not recommend** that 2-DG be placed on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.





# **2-deoxy-D-glucose (2DG) Topical Use for the Treatment of Herpes Simplex (HSV)**

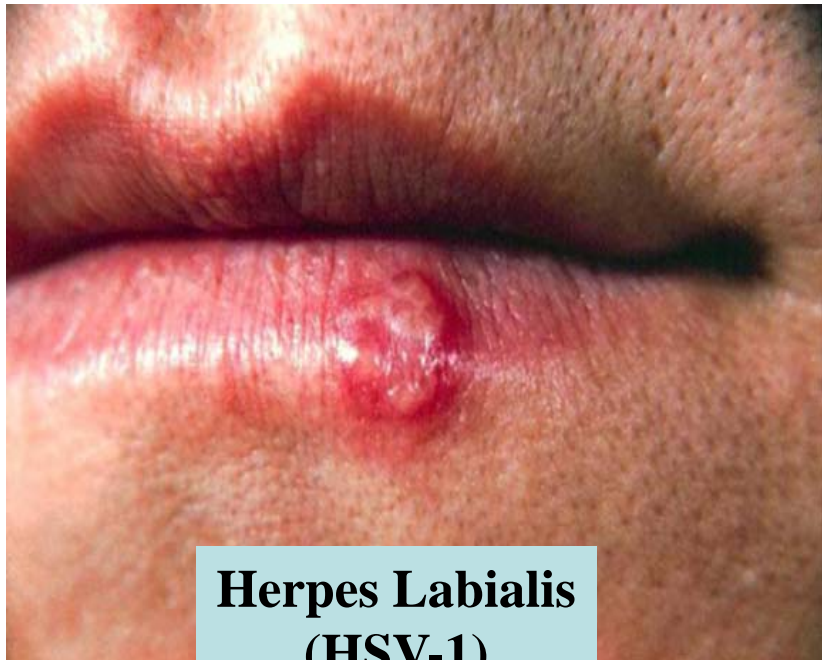
**Pharmacy Compounding Advisory Committee Meeting  
Oct 27, 2015**

**Jeffrey S. Murray, MD (Clinical Reviewer)  
Deputy Director  
Division of Antiviral Products**

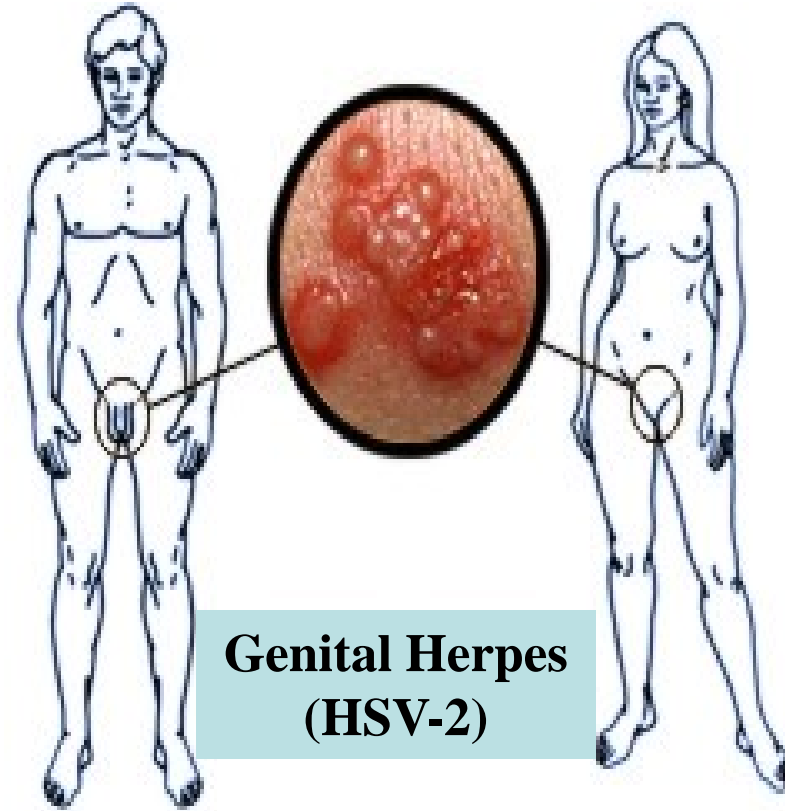
## HSV Infections: Overview

- **Serious infections:** neonatal HSV and HSV encephalitis, require systemic treatment
- **Most common infections:** initial and recurrent HSV lesions of the skin and oral mucosa, genital herpes and herpes labialis (cold sores) but also other areas of the skin.
- **Two HSV types:** 1 and 2; both susceptible to approved drugs
  - HSV-1 predominates in the oral region and HSV-2 in the genital region, but genital or oral herpes can be caused by either virus.
  - Herpes outbreaks are self-limiting (lasting days), but can be painful, temporarily disfiguring and stigmatizing. Some people have frequent recurrences. Herpes can be transmitted during or between outbreaks.

# HSV Infections: Overview



**Herpes Labialis  
(HSV-1)**



**Genital Herpes  
(HSV-2)**

## Products approved in the US for the treatment of genital and oral HSV

Product	Dosing	Indications
Acyclovir cream 5%	Multiple days	Herpes Labialis
Acyclovir ointment	Multiple days	Genital Herpes
Acyclovir buccal tablets	Single day	Herpes Labialis
Acyclovir/hydrocortisone cream	Multiple days	Herpes Labialis
Penciclovir cream 1%	Multiple days	Herpes Labialis
Docosonal cream 10%-- <b>OTC</b>	Multiple days	Herpes Labialis
Acyclovir Oral formulations	Multiple days	Genital Herpes
Famcyclovir Oral formulations	Single day Multiple days	Herpes Labialis Genital Herpes
Valacyclovir Oral formulations	Single day Multiple days	Herpes Labialis Genital Herpes

## 2DG: Efficacy Data Sources

Data that addresses the activity/efficacy of 2DG against HSV include:

- Published cell culture data and animal models
- One published clinical trial of topical 2DG for the treatment of genital HSV infection
- A few case series of patients with HSV treated with 2DG

## 2DG: Nonclinical Activity Data

- Cell culture data showed suppression of HSV-1 and HSV-2 in cell lines, but only at high concentrations.
- Cytotoxicity (cell death) not assessed so whether drug has antiviral activity vs. only a cytotoxic effect is not clear.
- Animal models of 2DG produced mixed results with positive results in some studies and no beneficial effects in others. Overall, more studies showed no effect.

## 2DG Clinical Trial – Blough and Giuntoli (JAMA 1979)

- “Randomized” controlled trial of 2DG as a 0.19% cream vs. placebo control in women with genital HSV lesions
- Cream administered 4 times daily, vehicle included miconazole
- 36 women received 2DG cream and 15 received placebo
- Authors claim a significantly shorter duration of herpetic lesions (10 day difference) and a reduction in the number of recurrences

## 2DG Clinical Trial: Blough and Giuntoli

- Experts wrote a letter to the editor (Corey 1980) questioning the trial conduct and results
- Trial did not appear to be randomized; more than twice as many received 2DG than placebo because randomization to placebo was limited due to unexplained “ethical issues”
- Corey states: possible toxicity of the placebo because the rate of healing on placebo was uncharacteristically long (twice historical rates) suggesting that placebo may have slowed healing
- Follow-up for recurrences was not well documented



## 2DG: Additional Clinical Efficacy Data and Safety

- Case Series of 2DG (Bierman 1983): no apparent beneficial effects
- Letter to editor (McCray 1982):
  - Case series of 22 patients who received 2DG for HSV: no effect
  - Placebo controlled study in 17 patients receiving 2DG 0.19% vs. placebo: no beneficial effect
- No mention of 2DG-related adverse events in Bough trial
- Unclear whether there were no adverse events or whether the article failed to report them
- No pharmacokinetic data to assess the extent of systemic absorption of 2DG

## 2DG: Historical Use in Compounding

- Data insufficient to quantify frequency of past or present use
- Appears to have been used topically for the treatment of genital HSV infections starting in the 1970s (around the time of the Blough publication)
- Enthusiasm for 2DG appeared to decline, according to review articles published in the 1980s, with the approval of acyclovir ointment in 1982, oral acyclovir in 1985, and many subsequent HSV antiviral drug approvals
- Internet searches: 2DG used for a variety of other conditions (not nominated): warts, diabetic neuropathy, dental rinses for oral ulcers

## 2DG: Conclusions

- Data are insufficient to fully evaluate safety or efficacy of 2DG for the treatment of HSV.
- Results of non-clinical data are mixed; most animal models show no beneficial effect.
- The only published clinical trial (1979) was of poor quality and largely discredited by HSV experts.
- Efficacy was not seen in subsequent clinical reports.
- Multiple safe and effective FDA approved drug (oral and topical) are available for the treatment of HSV infections.
- There is insufficient information on the extent of use of 2DG in compounding to evaluate the significance of its historical use.

## Recommendation

We do **not** recommend that 2-deoxy-D-glucose be placed on the list of bulk substances that may be used for compounding under section 503A of the FD&C Act for the treatment of herpes simplex infections.



# Alanyl-L-Glutamine

**Pharmacy Compounding Advisory Committee**

**October 28, 2015**

**Joyce Korvick, MD, MPH (Clin. Reviewer), Deputy Director for Safety  
Division of Gastroenterology and Inborn Errors Products (DGIEP)**



# Alanyl-L-Glutamine

## Review Team

**Joyce Korvick, MD, MPH (Clin. Reviewer), Deputy Director for Safety  
Wen-Yi Gao, MD (Clin. Reviewer), Medical Officer; and Ke Zhang, PhD  
(Nonclin. Reviewer), Pharmacologist, Division of Gastroenterology and  
Inborn Errors Products (DGIEP)**

**Hamid Shafiei, PhD (Pharmaceutical Quality Reviewer), Office of  
Pharmaceutical Quality**

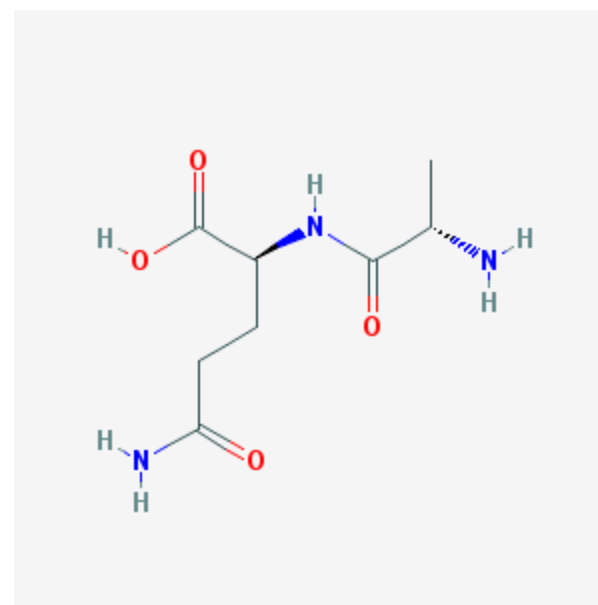


## Alanyl-L-Glutamine

We reviewed the nomination for intravenous use as nutritional support in critically ill and to reduce the rate of infectious complications in surgically and critically ill patients.

# Alanyl-L-Glutamine – Physical and Chemical Characterization-1

- **Formula:** C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>
- **Molecular Weight:** 217.22 g/mol
- **Melting Point:** 215-222 °C
- **Crystal Forms:** This API is described as a white to off-white powder.
- **Solubility:** Soluble in water
- **Stability:** The storage condition recommended by suppliers is “Store at 2°C - 8°C. It is claimed to be more stable than L-glutamine at ambient conditions.
- **Structure Characterization:** chemical entity is well characterized





# Alanyl-L-Glutamine – Physical and Chemical Characterization-2

- Possible synthetic route
  - Multiple methods/routes of manufacture are reported including chemical, enzymatic, and *E. coli* fermentation processes.
  - This dipeptide is produced as a solid.
  - It is intended for compounding into a solution dosage form for IV infusion.
- Likely impurities
  - Amino acids, other dipeptides and polypeptides
  - Residual organic solvents and reagents used in manufacturing and purification processes
  - Heavy metal/elemental impurities from starting material and agents used in process
  - Bioburden (e.g., bacteria, fungus, virus when produced by fermentation)
  - Endotoxin

## Alanyl-L-Glutamine – Physical and Chemical Characterization-3: Conclusions

- Alanyl-L-glutamine is a well-characterized chemical entity.
- The types and levels of potential impurities of this chemical entity can vary depending on starting material, reagent, and manufacturing process.
- The quality cannot be adequately assessed due to lack of information regarding the manufacturing of alanyl-L-glutamine from suppliers of this chemical entity.
  - Key safety concern: Lack of established quality standard for the API intended for compounding into *large volume parenteral formulations for repeated intravenous administration to compromised patients with severe underlying illnesses*

# Alanyl-L-Glutamine - Nonclinical Assessment-1

- Pharmacology
  - There is rapid conversion of alanyl-L-glutamine to L-alanine and L-glutamine following infusion.
  - Glutamine is a non-essential amino acid and is abundant in blood and intracellular tissue.
  - Glutamine plays an important role in a number of physiologic functions, such as protein synthesis, immune cell growth, maturation, and function.
  - Glutamine levels may decrease in severely ill patients with high catabolic states and patients with impaired ability to absorb glutamine.
- Safety pharmacology: No studies on CNS, cardiovascular, or respiratory function are available.

## Alanyl-L-Glutamine - Non-Clinical Assessment-2

- Acute toxicity
  - No treatment-related adverse effects in Sprague-Dawley rats with single oral doses up to 2000 mg/kg
- Repeat dose toxicity
  - The results of a 14-day, oral, dietary, dose-ranging study conducted with alanyl-L-glutamine in male and female CD Sprague-Dawley rats at 0, 1, 3, and 5% (w/w in feed) revealed no clear treatment-related adverse effects at doses up to 5% (Oda, 2008).
  - The results of a 13-week, oral, dietary, toxicity study conducted with alanyl-L-glutamine in male and female CD Sprague-Dawley rats at 0, 1, 3, and 5% (w/w in feed) revealed no clear treatment-related adverse effects at doses up to 5%, suggesting that the highest dose of 5% (3129 mg/kg for males or 3601 mg/kg for females) was the no observed adverse effect level (NOAEL) (Oda, 2008).

## Alanyl-L-Glutamine - Nonclinical Assessment-3

- Mutagenicity: Not mutagenic or clastogenic in Ames test or an in vitro Chinese hamster lung cell model
- Developmental and reproductive toxicity: No information from animals studies is available
- Carcinogenicity: No information from animal studies is available
- Toxicokinetics: No information from animal studies is available
- Other relevant toxicology studies
  - DL-Alanine was shown to be tolerated at extremely high dietary levels (5, 10, and 20%) in a 26-week study in rats (Chow, 1976).

## Alanyl-L-Glutamine - Nonclinical Assessment-3: Conclusions

- Alanyl-L-glutamine was well tolerated in rats at high dietary levels (up to 5%) for 13 weeks.
- No intravenous animal toxicity studies are available.

## Alanyl-L-Glutamine – Human Safety Data-1

- Concerns related to intravenous administration of bulk compounded parenteral product
  - Potential impurities (heavy metals, microbes, endotoxin, solvents used in manufacture)
- Adverse reactions: Similar to the safety profile of glutamine
  - Caution is needed when administered to patients with liver and kidney disease.
  - Patients with defects in amino acid metabolism may be at greater risk for hyperammonemia and CNS toxicity.

## Alanyl-L-Glutamine – Human Safety Data-2 (FAERS – FDA Adverse Events Reporting System)

- Search terms used: Alanyl-glutamine, glutamine, L-glutamine, NutreStore (product name)
- “All” records up to August 2, 2015
- Alanyl-glutamine
  - 3 foreign reports with use of IV alanyl-glutamine
    - one patient died of a cardiac arrest following an overdose of anesthesia during surgery, and two patients had chills, dyspnea, and fever associated with concomitant administration of multiple parenteral nutrition products, such as lipids, dextrose, amino acids, and alanyl glutamine.



# Alanyl-L-Glutamine – Human Safety Data-3 (FAERS report, *cont.*)

## Glutamine

- 83 unduplicated adverse event reports with the use of intravenous and/or oral glutamine (72 reports, concomitant drugs)
- 11 cases, no concomitant drug use reported
  - Fatal cases: 7 unique death cases listed the cause of death as cancer (n=3), stroke (n=1), unknown (n=3); two of the seven had a documented history of cancer.
  - Non-fatal cases
    - 1 hospital admission for upset stomach and vomiting
    - 1 reported sickle cell crisis while taking glutamine

## Alanyl-L-Glutamine – Human Safety Data-4 (CAERS – CFSAN Adverse Event Reporting System)

- Search Terms: dietary supplements. The system does not have standard product names.
- 49 spontaneous reports from May 1995 to February 2015
- 33 cases were documented to have taken oral product containing glutamine
  - No fatalities reported
  - Reported adverse reactions
    - vomiting, diarrhea, abdominal pain, pruritus, rash, erythema multiforme, flushing, face edema, swelling face, dry eye, blister, abnormal liver function tests, jaundice asthma, urine blood, dizziness, tremor, insomnia, and pyrexia

# Alanyl-L-Glutamine – Human Safety Data-5

(A randomized trial of glutamine and antioxidants in critically ill patients)

- Randomly assigned 1,223 critically ill adults
- 40 intensive care units (ICUs) in Canada, the U.S, and Europe
- Patients had multi-organ failure receiving mechanical ventilation
- 611 adult patients received approximately 65 g of glutamine supplements daily
  - 50% of dose intravenously as alanyl-glutamine
  - 50% of dose orally as alanyl-glutamine and glycine-glutamine

*(Heyland et al) N Engl J Med 2013;368:1489-97.*

## Alanyl-L-Glutamine – Human Safety Data-6

- Adverse events: 52 serious adverse events in 46 patients
  - 4 considered to be potentially related to study drug
  - No significant differences in rates across groups
- Elevated serum urea levels ( $> 50$  mmol per liter): Was higher among the patients who received glutamine as compared with those who did not (13.4% vs. 4.0%).

## Alanyl-L-Glutamine – Human Safety Data-7

- 28-day mortality: Higher in alanyl-L glutamine treated patients than comparator arm
  - 32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% CI, 1.00 to 1.64;  $p = 0.05$ 
    - *Authors state that a p-value of less than 0.044 was considered to be statistically significant for the mortality analyses.*
- In-hospital mortality: Higher in the alanyl-L-glutamine treated patients than comparator
  - 37.2% vs. 31.0%,  $p < 0.02$
- Mortality at 6 months: Higher in the alanyl-L-glutamine treated patients than comparator
  - 43.7% vs. 37.2%,  $p < 0.02$

## Alanyl-L-Glutamine – Human Safety Conclusions

- 2015 update of the Canadian Practice Guidelines recommends that “parenteral supplementation with glutamine NOT be used,” based in part on the mortality results from the Heyland trial.
  - Data suggest glutamine supplementation should not be given at high doses (>0.5 g/kg/day) or early in the acute phase of critical illness in patients with multiple organ failure or un-resuscitated shock requiring significant vasopressor support.
- Recent Cochrane review (2014) shows little effect on risk of mortality or length of ICU stay with glutamine supplementation (53 studies of 4,671 patients).
- Concerns about the safety of bulk substance and potential toxicity from contaminants for use as intravenous formulation
  - Heavy metals, microbes, endotoxins, residual solvents

## Alanyl-L-glutamine – Clinical Effectiveness-1

- Literature review of the evidence of the effectiveness of glutamine supplementation in the treatment of patients with critical illness or undergoing elective major surgery
- Trials that studied glutamine or alanyl-L-glutamine were included.
- Focused review on 4 published literature reviews:
  - A.S.P.E.N. position paper (Vanek, 2011);
  - Cochrane Review (Tao, 2014);
  - Wischmeyer et al., review (2014)
  - The Canadian Clinical Practice Guidelines (2015)
    - *These publications included multiple clinical trials generally small in size, with varying results.*
- One large, randomized trial (Heyland 2013)

## Alanyl-L-glutamine - Clinical Effectiveness-2

### Cochrane Review: Summary of Outcomes Glutamine-supplemented vs. Non-Supplemented nutrition critically ill (adapted from Cochrane Review (2013))

OUTCOMES	RELATIVE EFFECT	# of PATIENTS (# of Studies)	QUALITY OF EVIDENCE
Infectious complications	RR 0.79 (0.71 to 0.87)	2303 (33 studies)	Moderate <sup>1</sup>
Short-term mortality (within hospital stay or closest to one month)	RR 0.89 (0.78 to 1.02)	3454 (36 studies)	Low <sup>1,2</sup>
Long-term mortality (closest to six months)	RR 1.0 (0.89 to 1.12)	2277 (11 studies)	Moderate <sup>2</sup>
Length of hospital stay (mean)	Glutamine: 3.46 days shorter	2963 (36 studies)	Low <sup>2,3</sup>
Length of ICU stay (mean)	Glutamine: 0.18 days <b>longer</b>	2284 (22 studies)	Moderate <sup>2</sup>
Days on mechanical ventilation (mean)	Glutamine: was 0.69 days lower	1297 (14 studies)	Moderate <sup>2</sup>

<sup>1</sup>Publication bias is suspected as smaller studies with outcomes favoring non-supplemented patients were lacking

<sup>2</sup>The proportion of high risk of bias trials in this outcome was higher than 30%, the potential limitations are likely to reduce confidence in the estimate of effect

<sup>3</sup>There was substantial variability in effect estimates ( $I^2 = 63\%$ )

<sup>4</sup>The 95% CI of the pooled estimate was not narrow enough for a confident judgment of the effect size



## Alanyl-L-glutamine–Clinical Effectiveness-3

Summary of Key Findings of Meta-Analyses and RTC Study				
Studies	Cochrane	Wischmeyer	CANADIAN*	Heyland
<b>Mortality</b>	No impact:  Short term (LOW) Long term (MODERATE)	Overall Favorable (trend, NS*)  Short term (in hospital) Favorable; statistically significant.	Overall favorable; (trend, NS)  Short term (in hospital) Favorable; statistically significant	<u>Negative</u> impact;  Day-28: trend (NS)  In hospital & 6- month: statistically significant
<b>Infection</b>	Favorable; statistically significant (MODERATE)	Favorable; NS	Favorable; NS	NA
<b>Length of Hospital Stay</b>	Favorable; statistically significant (LOW)	Favorable; statistically significant	Favorable; statistically significant	No difference
<b>Length of ICU stay</b>	Worsened; statistically significant (MODERATE)	Favorable; NS	Favorable; NS	No difference
<b>Mechanical Ventilation</b>	Favorable; statistically significant (MODERATE)	Favorable; NS	Favorable; NS	No difference
<b>Serious adverse events</b>	Worse; NS (MODERATE)	NA	NA	No difference (excluding mortality)

*Note most studies included in the Canadian recommendations are included in the Wischmeyer review [for details see backgrounder]. \*NS= not statistically significant*

## Alanyl-L-glutamine – Clinical Effectiveness-4

- Majority of studies included in the Cochrane review were small. Three quarters had sample sizes fewer than 100, and the vast majority of those had sample sizes under 50.
- Over half of the studies included in Wischmeyer and Canadian reviews had sample sizes <100.
- Varying outcome results and of varying quality (within the meta-analysis and across meta-analyses)
- On the other hand, the negative effect of glutamine supplementation was reported for in-hospital mortality and mortality at 6 months in a large (N=1218; glutamine: 611, and no glutamine: 607), randomized, multi-center study (Heyland 2013).

## Alanyl-L-glutamine - Clinical Effectiveness-5

- Is the product compounded with this bulk drug substance intended to be used in a serious or life-threatening disease?
  - Yes. The product is intended to be used in critically ill ICU patients.
- Are there alternative approved therapies that may be as effective or more effective?
  - Although not FDA-approved for intravenous administration, glutamine is a component of an approved product and the subject of a USP monograph, and therefore can be used in compounding under section 503A of the FD&C Act.

## Alanyl-L-glutamine – Clinical Effectiveness Conclusions

- Supplementation of parenteral glutamine may improve clinical outcomes when given to appropriate patients as part of complete nutrition support; however, this has not been persuasively established.
- The timing of administration, dosage, and specific subset of critically ill patients for whom glutamine supplementation might be beneficial has not been determined and requires further study.
- Significant risk-benefit evaluation is necessary given these knowledge gaps in conjunction with recent data from Heyland et al., which suggest glutamine supplementation increased mortality in critically ill patients.

## Alanyl-L-Glutamine – Historical Use in Compounding

- Length of time substance has been used in pharmacy compounding
  - Use of glutamine has been reported in the literature since 1990 (Souba, 1990).
  - Alanyl-L-glutamine has been used in compounding for parenteral use for at least 12 years (Goeters, 2002).
- Medical conditions it has been used to treat
  - It has been used to treat critically ill ICU patients with trauma, surgeries, pneumonia, renal disorders, hemodialysis, liver disorders, infections, and coma.
- How widespread is its use
  - Alanyl-L-glutamine has been used in ICUs in the US.

## Recommendation

In light of the above effectiveness considerations and given the safety concerns surrounding potentially toxic impurities in parenterally administered alanyl-L-glutamine in chronically ill patients, and in conjunction with the increased mortality observed in a large, randomized controlled trial — *we do not* recommend that alanyl-L-glutamine be placed on the list of bulk substances that may be used for compounding under section 503A of the FD&C Act.



# Glutaraldehyde

## Pharmacy Compounding Advisory Committee Meeting October 28, 2015

**Hon-Sum Ko, MD, FACP (Clin. Reviewer), Medical Officer  
Division of Dermatology and Dental Products**



# Glutaraldehyde

## Review Team

**Hon-Sum Ko, MD, FACP (Clin. Reviewer), Medical Officer  
Division of Dermatology and Dental Products**

**Sam Bain, PhD (Chem. Reviewer), Chemist  
Office of Pharmaceutical Quality**

**Jiaqin Yao, PhD (Pharmacology Reviewer), Pharmacologist  
Division of Dermatology and Dental Products**

**Doanh Tran, PhD (Clin. Pharmacology Team Leader), Pharmacologist  
Division of Clinical Pharmacology, III**



# Glutaraldehyde

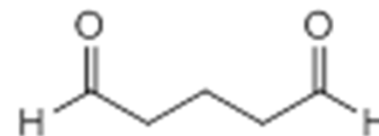
- Glutaraldehyde has been nominated to be placed on the list of bulk drug substances that can be used to compound under section 503A of the FD&C Act for the following proposed uses:
  - For the treatment of warts
  - As a soaking solution for heart valve repairs

# Glutaraldehyde for Cutaneous Warts

- Glutaraldehyde is applied to warts as a topical formulation (usually a solution).
- It may act via chemical dehydration causing superficial tissue necrosis.

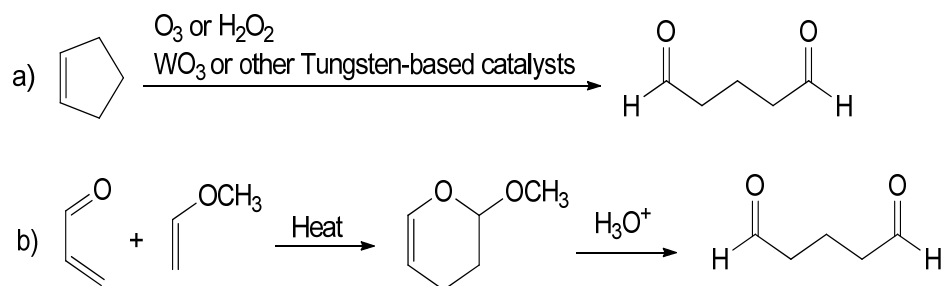
# Physical and Chemical Characterization-1

- Formula:  $C_5H_8O_2$
- Molecular Weight: 110.117
- Density: 1.06 g/mL
- Liquid at room temperature, boiling at about  $188\text{ }^{\circ}\text{C}$ , with decomposition.



## Physical and Chemical Characterization-2

- Two possible routes of synthesis



- Likely Impurities: Starting materials and possible air oxidation products (glutaric acid and 5-oxopentanoic acid)
- Conclusion: Glutaraldehyde is well-characterized physically and chemically. From chemical synthesis and stability perspectives, compounding glutaraldehyde as a topical product is reasonable, when stored protected from heat and air.

# Nonclinical Assessment-1

## Pharmacology

- Immediate superficial tissue necrosis by chemical dehydration

## Safety Pharmacology

- Adverse effects on CNS, cardiovascular, and respiratory systems following systemic exposure

## General Toxicology

- Local irritation of the skin, eye, and respiratory tract, exacerbated by repeated exposure

## Nonclinical Assessment-2

### Mutagenicity

- DNA-protein cross-linker: mutagenicity positive in vitro, but negative in vivo

### Developmental and Reproductive Toxicity

- No reproductive and developmental effects seen in tested animals

### Carcinogenicity

- Not carcinogenic in rats and mice

### Special Toxicology

- Skin sensitizer

# Human Pharmacokinetics

- No reports of human pharmacokinetic studies in vivo
- In vitro data suggest that glutaraldehyde solution can absorb into and bind to skin tissue, but only a small fraction would pass through the skin and be available for systemic distribution.

# Human Safety-1

## Adverse Reactions

- As an irritant: irritation to respiratory and dermatologic systems via vapor or direct contact, respectively, and thus an occupational hazard to workers exposed to the substance in their environment
- As a sensitizer: allergic contact dermatitis
- In clinical use: skin ulceration and necrosis



## Human Safety-2

### Clinical Trials

- Human dermal safety studies: phototoxicity and photo-allergenicity not demonstrated; low sensitization potential and irritancy potential
- No randomized controlled trials to determine safety of glutaraldehyde
- Available safety data from open-label studies or case reports: pigmentary changes, irritation, allergic contact dermatitis and skin ulceration/ necrosis as adverse reactions, especially with high concentrations of glutaraldehyde (e.g., 20%)

## Efficacy in Treatment of Warts

- One report of a small controlled clinical trial (N=81) comparing glutaraldehyde 10% solution to salicylic acid/lactic acid paint in plantar warts: comparable results (44% to 47% cure rates)
- Reported open label trials (1971 – 1994): varying degrees of efficacy (71% to 100% cure rates)

# Historical Use in Compounding

- The use of glutaraldehyde compounded for medical use has included:
  - Plantar hyperhidrosis (1968)
  - Onychomycosis (1970)
  - Cutaneous warts (since the 1970s)
- Conclusion: It is a viable option for treatment of cutaneous warts: its use appears widespread, with approved formulations in some countries.

# Conclusions

- Glutaraldehyde is well characterized in its physical and chemical properties.
- For topical use, glutaraldehyde may cause pigmentation changes, allergic contact dermatitis, skin ulceration and necrosis, especially with high concentrations; these risks may be managed by the use of strengths of 10% or lower.
- There is evidence of efficacy in the treatment of warts based primarily on open-label studies.
- It has been used for cutaneous warts for over 40 years, and the practice is world-wide.

# Recommendation

We recommend that glutaraldehyde for topical use be placed on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.



# Glycyrrhizin

## **Pharmacy Compound Advisory Committee Meeting October 28, 2015**

**Sarah Connelly, MD, Medical Officer, Division of Antiviral Products  
(DAVP)**



# Glycyrrhizin

## Review Team

**Sarah Connelly, MD, Medical Officer, Division of Antiviral Products (DAVP)**

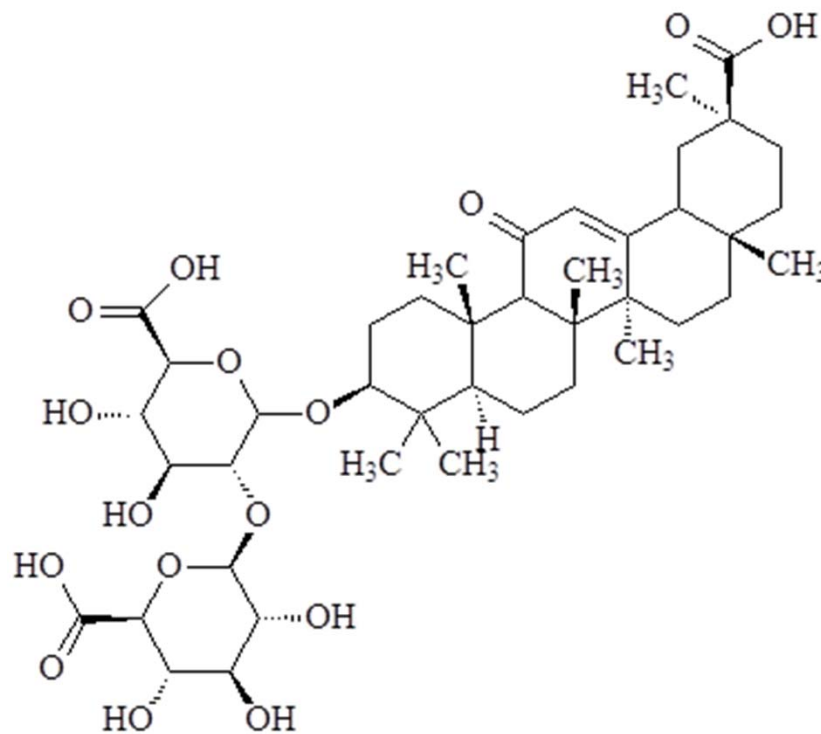
**Mark Powley, PhD, Pharmacology/Toxicology Reviewer, DAVP**

**William Ince, PhD, Clinical Virology Reviewer, DAVP**

**George Lunn, PhD, Product Quality Reviewer, Office of Pharmaceutical Quality (OPQ)**

# Chemistry

Glycyrrhizin (also known as glycyrrhizic acid or glycyrrhizinic acid) is extracted from *Glycyrrhiza glabra*.





# Quality

- NF Grade Ammonium Glycyrrhizate
  - Well characterized with tests for assay (78.0-102.0%), impurities, identity, residue on ignition, optical rotation, and water
- Other preparations such as Chinese traditional medicines or USP Dietary Supplement Monographs for powdered licorice
  - Low glycyrrhizin assay values
  - Poorly characterized with regard to impurities
  - May contain other pharmacologically active compounds, such as morphine, ephedrine, pseudoephedrine, methylephedrine, amygdalin

# Glycyrrhizin

## Non-Clinical Safety (1)

- **Primary Pharmacology:** Antiviral activity has not been adequately demonstrated. Selectivity indices for HCV and other viruses were generally estimated to be  $<10$ , consistent with a lack of a significant antiviral effect.
- **Secondary Pharmacology:** Inhibition of  $11\beta$ -hydroxysteroid dehydrogenase-2 ( $11\beta$ -OHSD2) in the kidney is a concern.
- **Safety Pharmacology:** No effects detected on cardiovascular, respiratory, or gastrointestinal systems of cats given single intraperitoneal dose of glycyrrhetic acid.

# Glycyrrhizin

## Non-Clinical Safety (2)

- Acute Toxicology: LD<sub>50</sub> for glycyrrhizinic acid and various salts in mice, guinea pigs, and dogs in the range of 308 to 12,700 mg/kg
  - Intravenous administration of ammoniated glycyrrhizin in mice resulted in convulsions and hemolysis.
- Repeat-Dose Toxicology
  - High oral doses of glycyrrhizinic acid and/or its monoammonium salt in rats and mice led to apparent mineralocorticoid excess or pseudo-hyperaldosteronism.
  - Oral doses of glycyrrhizin crude extract caused myolysis of heart papillary muscles in rats.

# Glycyrrhizin

## Non-Clinical Safety (3)

- Mutagenicity: Weight of evidence suggests glycyrrhizinic acid and related salts are not genotoxic.
- Developmental and Reproductive Toxicology: Weight of evidence suggests glycyrrhizinic acid and its salts are not teratogenic.
- Carcinogenicity: No effects detected in mice administered oral disodium salt of glycyrrhizinic acid for 96 weeks.
- Toxicokinetics
  - Orally administered glycyrrhizinic acid is hydrolyzed in the gastrointestinal tract to form glycyrrhetic acid, which is then readily absorbed.
  - Intravenous administered glycyrrhizinic acid is metabolized in the liver, excreted via bile, and subsequently metabolized to glycyrrhetic acid in the gastrointestinal tract.

# Glycyrrhizin

## Non-Clinical Safety: Conclusions

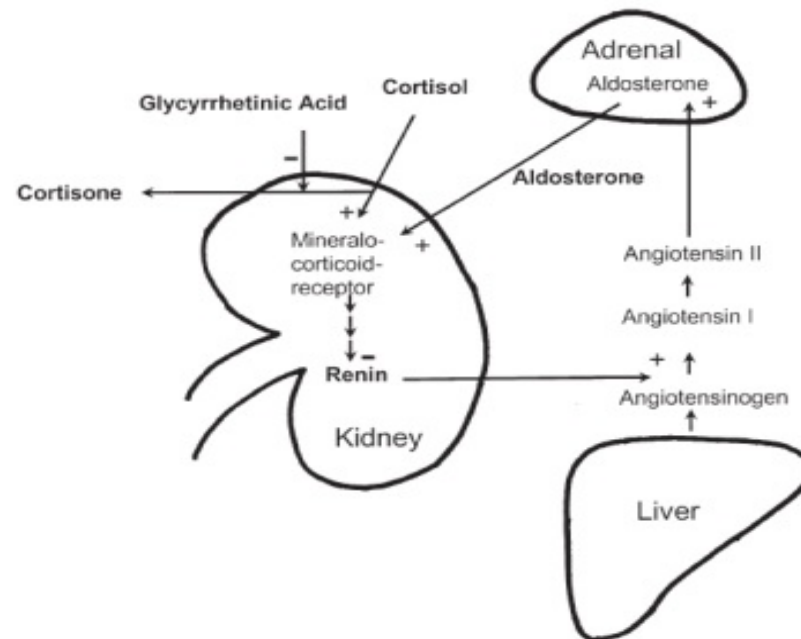
- Non-clinical data appear to support the safety of low-level exposures to glycyrrhizinic acid through oral routes (e.g., diet); however, there is little non-clinical data for intravenous glycyrrhizinic acid administration.
- A primary concern is the potential for off-target effects related to inhibition of  $11\beta$ -OHSD2.
- Convulsions occurring following intravenous dosing in mice may also be relevant for clinical administration.

# Glycyrrhizin

## Human Safety Data – Adverse Reactions

Pseudo-hyperaldosteronism effects most commonly characterized

- Related to glycyrrhizin's inhibition of conversion of cortisol->cortisone
- Elevated cortisol levels in the kidney stimulate the mineralocorticoid receptor with effects such as sodium retention, edema, hypokalemia, and hypertension



# Glycyrrhizin

## Human Safety Data – Adverse Reactions (2)

- Medline search for “licorice” reveals >100 case reports describing events related to pseudo-hyperaldosteronism including
  - hypokalemia, hypertension, edema, myopathies with some further serious cases of rhabdomyolysis, torsades de pointes, paralysis, posterior reversible encephalopathy syndrome, cardiac arrest
- Glycyrrhizin dose typically not available

# Glycyrrhizin

## Human Safety Data - Adverse Reactions (3)

### Adverse Reactions in Chronic Hepatitis C population

- Patients with predisposing sodium-retaining conditions, such as ascites and hypertension, which occur with chronic HCV, may be more susceptible to glycyrrhizin's pseudo-hyperaldosterone effects.



# Glycyrrhizin

## Human Safety Data - Adverse Reactions (4)

*Figure 2: Most frequent glycyrrhizin-related adverse events in patients with chronic HCV infection during 12-week double-blind treatment*

	5×/week GL N = 123	3×/week GL N = 127	Placebo N = 129
Number of subjects	123	127	129
Number of subjects with AEs	57	48	35
Number of AEs	138	101	82
Relationship possible (N, %)			
Hypertension aggravated	12 (8.7%)	1 (1.0%)	4 (4.9%)
Hypertension NOS*	7 (5.1%)	4 (4.0%)	–
Headache	5 (3.6%)	6 (5.9%)	1 (1.2%)
Abdominal pain, upper	1 (0.7%)	2 (2.0%)	6 (7.3%)
Paraesthesia	2 (1.4%)	4 (4.0%)	–
Blood pressure increased	1 (0.7%)	3 (3.0%)	2 (2.4%)
Relationship probable (N, %)			
Hypertension NOS	6 (4.3%)	5 (5.0%)	–
Paraesthesia	5 (3.6%)	5 (5.0%)	–
Hypokalaemia	5 (3.6%)	3 (3.0%)	–

SAF: safety analysis set, GL: glycyrrhizin

\*NOS: Not otherwise specified.

*Source: Manns MP, Wedemeyer H, Singer A, Khomutjanskaja N, Dienes HP, Roskams T, Goldin R, Hehnke U, and Inoue H; European SNMC Study Group. Glycyrrhizin in patients who failed previous interferon alpha-based therapies: biochemical and histological effects after 52 weeks. J Viral Hepat. 2012 Aug;19(8):537–46.*

# Glycyrrhizin

## Efficacy: Chronic Hepatitis C

- No clinically meaningful antiviral effect, as measured by HCV RNA, was demonstrated using intravenous glycyrrhizin for the treatment of chronic HCV infection in 8 identified clinical trials.
- Some trials have shown a decrease in ALT levels, which was not sustained following treatment cessation.
- Several meta-analyses have concluded that there are scientifically insufficient data on glycyrrhizin therapy to evaluate its usefulness (Coon J and Ernst E, 2004; Dhiman RK, Chawla YK, 2005; Levy C et al., 2004; Stickel F and Schuppan D, 2007).
  - Stickel and Schuppan’s 2007 paper states the “treatment of liver disease with glycyrrhizin, regardless of the aetiology, cannot be advocated due to the lack of obvious benefit.”

# US Approved Therapies for Treatment of Chronic Hepatitis C Infection

Currently approved oral HCV direct acting antiviral treatment options include the fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without ribavirin; the fixed-dose combination ledipasvir/sofosbuvir; and sofosbuvir plus simeprevir.

- Demonstrated antiviral efficacy with sustained virologic response (SVR) rates exceeding 90% in many populations; achieving SVR is considered a virologic cure of chronic HCV.
- Across “numerous phase 3 programs, less than 1% of patients without cirrhosis discontinued treatment early, and AEs were mild. Most AEs occurred in RBV-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials), but still very low.”<sup>1</sup>
- Removes risks of intravenous administration (e.g., phlebitis, infection)

<sup>1</sup> American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C, are available at <http://www.hcvguidelines.org/>. Accessed Sept. 4, 2015.

# Glycyrrhizin

## Efficacy: Chronic Hepatitis B

- Four trials of intravenous glycyrrhizin in the treatment of chronic hepatitis B infection identified
  - Two trials were small pilot studies that also included approved treatments for chronic hepatitis B (interferon, lamivudine) confounding the results.
  - Two trials describe an effect on aminotransferases, though do not demonstrate an effect on HBV serologies.
- Therefore, these studies do not provide convincing evidence for use of intravenous glycyrrhizin in the treatment of chronic hepatitis B.

## Glycyrrhizin Efficacy: HIV

A review article on the antiviral effects of glycyrrhiza species by Fiore et al., (2008) describes two studies of glycyrrhizin use in HIV patients where some patients were stated to have achieved increased CD4 cell counts.

Notably, both referenced studies are from Japan and were conducted in the 1980s before the availability of highly active antiretroviral therapy and, thus, do not provide evidence for any beneficial use of intravenous glycyrrhizin in the treatment of HIV (Gotoh Y et al., 1987; Mori K et al., 1989).

# Glycyrrhizin

## Historical Use in Compounding

- Use of Glycyrrhiza species (licorice) dates back to ancient manuscripts from China, India, and Greece and has been in use for curative and flavoring purposes for more than 4,000 years.
- Literature suggests that glycyrrhizin has been used for more than three decades to treat chronic hepatitis in Japan (Davis et al., 1991; Fiore et al., 2008).
- Use of intravenous glycyrrhizin in pharmacy compounding in the United States is unknown based on review of published literature.

## Glycyrrhizin: Conclusions

- Glycyrrhizin is not an antiviral compound by our definition, and intravenous glycyrrhizin has no demonstrable antiviral effect in clinical studies of patients with chronic HCV infection — *in contrast to the significant efficacy of available, approved all oral HCV DAA combination therapies.*
- Likewise, data for intravenous glycyrrhizin in the treatment of chronic hepatitis B and HIV have not demonstrated efficacy.
- Re safety considerations, the association between glycyrrhizin use and serious pseudo-hyperaldosteronism-related adverse reactions is well established, and patients with chronic HCV infection may be more susceptible to glycyrrhizin's pseudo-hyperaldosterone effects.
- We were unable to find any evidence of the history or extent of the use of glycyrrhizin in compounded drug products in the US, either to treat chronic HCV infection or for other uses.

## Recommendation

We do **not** recommend that intravenous glycyrrhizin be included on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.





# Domperidone

## Pharmacy Compounding Advisory Committee Meeting October 28, 2015

**Catherine Sewell, MD, MPH (Clin. Reviewer) and Leslie McKinney, PhD  
(Nonclin. Reviewer) Division of Bone, Reproductive, and Urologic Products**

**Anil Rajpal, MD (Clinical Reviewer)  
Division of Gastroenterology and Inborn Errors Products**



# Domperidone

## Review Team

**Catherine Sewell, MD, MPH (Clin. Reviewer) and Leslie McKinney, PhD (Nonclin. Reviewer)**  
**Division of Bone, Reproductive, and Urologic Products**

**Anil Rajpal, MD (Clinical Reviewer)**  
**Division of Gastroenterology and Inborn Errors Products**

**Ben Zhang, PhD (Pharmaceutical Quality Reviewer)**  
**Office of Pharmaceutical Quality**

**Christine Garnett, PharmD (Clinical Analyst)**  
**Division of Cardiovascular and Renal Products**

**Joel Weissfeld, MD, MPH (Medical Officer) and Mohamed Mohamoud, PharmD, MPH**  
**(Drug Utilization), Division of Epidemiology II**

**Miriam Chehab, PharmD (Safety Evaluator) and Ali Niak, MD (Medical Officer)**  
**Division of Pharmacovigilance II**

# Overview

## Mechanism of action

- blocks dopamine receptors in the gut to increase gut motility
- blocks dopamine receptors in the pituitary, increases prolactin secretion to affect milk production

## Primary use in compounding

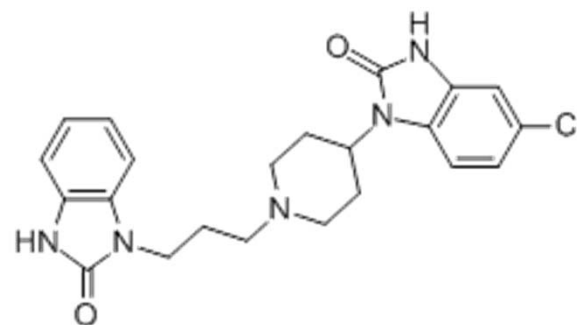
- gastrointestinal conditions (e.g., gastroparesis, nausea and vomiting)
- lactation disorders

# Outline

- Physical and chemical characterization
- Historical use in compounding
- Efficacy: gastrointestinal and lactation disorders
- Safety
  - Basics - QT interval and arrhythmia risk
  - Domperidone regulatory history – QT prolongation/arrhythmia risks
  - Nonclinical evidence
  - Clinical evidence
- Conclusions/Recommendation

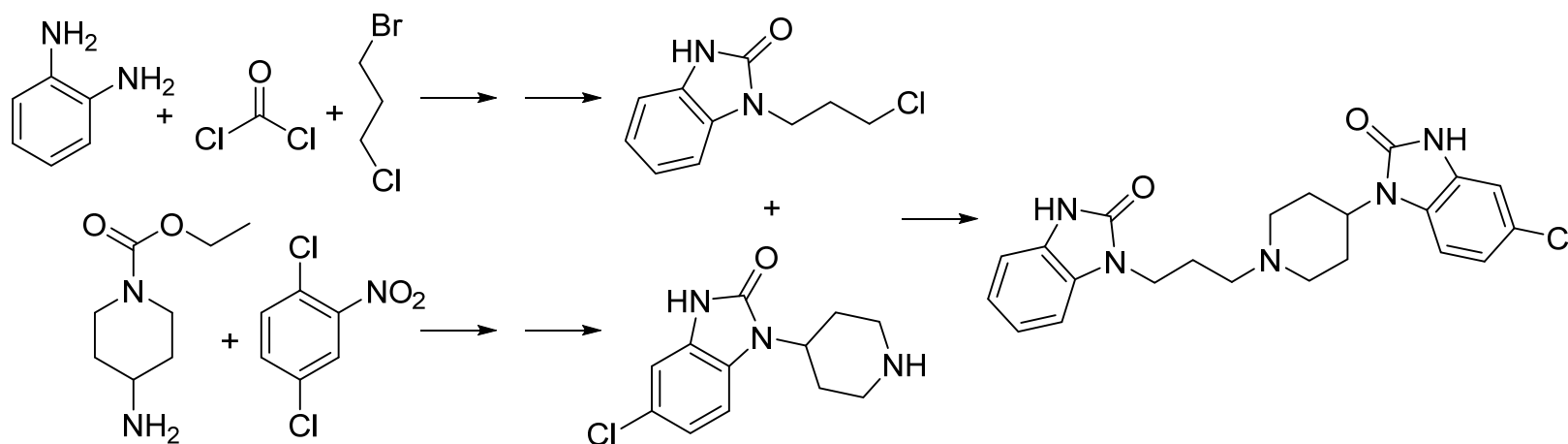
# Physical and Chemical Characterization

- **Formula:**  $C_{22}H_{24}ClN_5O_2$
- **Molecular Weight:** 425.911 g/mol
- **Melting Point:** 242 - 243 °C
- **Solubility:** Slightly soluble in water
- **Stability:** Stable in solid forms under ordinary storage conditions.  
Aqueous solutions may degrade when exposed to sunlight.
- **Structure Characterization:** Well Characterized



# Physical and Chemical Characterization, *cont.*

- **Possible synthetic route**



- **Likely Impurities:** starting materials, reaction intermediates and byproducts

**Conclusion:** domperidone is a synthetic small molecule, and it is stable under ordinary storage conditions.

# Historical Use in Compounding

- Not approved for any indication in the U.S.
- Approved outside the U.S. since 1978 to treat certain gastrointestinal conditions
  - Prior to 2014: maximum daily dose 80 mg/day
  - As of 2014: maximum daily dose 30 mg/day up to 7 days of treatment
- Used as galactagogue to increase breast milk supply
  - In doses of 30 mg up to 120 mg/day
  - This use is not approved in any country

# Domperidone Utilization Data

FDA drug utilization review from June 2009-May 2015 shows:

- Dispensed Prescriptions
  - Between 7,500 to 11,600 prescriptions dispensed/year in the US<sup>1</sup>
  - Primarily dispensed to women (77% of total prescriptions) \*
    - 20% of prescriptions to women 20-39 years
    - 26% of prescriptions to women 40-59 years
  - 60% of total prescriptions prescribed by gastroenterologists;
    - 6% by obstetrician/gynecologists
- Office-Based Physician Survey Data
  - Most commonly reported indication: gastroparesis<sup>2</sup>

\*June 2012 -May 2015

1. Data Source: IMS, National Prescription Audit (NPA).™ June 2009- May 2015. Extracted July 2015

2. Data Source: Encuity Research, LLC, Treatments Answers Audit.™ June 2009- May 2015. Extracted July 2015





# Efficacy

## Gastrointestinal Conditions Lactation Disorders

# Efficacy: Gastrointestinal Conditions

- **Gastroparesis – 3 trials**

1. Randomized, withdrawal, placebo-controlled, 4-week trial - diabetic gastroparesis (N= 208)
  - 54% lower total symptom score (TSS) with domperidone 20 mg PO QID (n=105) vs. placebo (n=103) (p=0.025)\*,#
  - TSS = sum of investigator-assessed five scores ranging from 0 to 3 for: nausea, vomiting, early satiety, abdominal distention/bloating, and abdominal pain

\*Camilleri et al., 2013

#Silvers et al., 1998

## Efficacy: Gastrointestinal Conditions, *cont.*

2. Randomized, active-controlled, 4-week trial - diabetic gastroparesis (n= 95)
  - treatment arms = Domperidone 20 mg PO QID (n=48) and metoclopramide 10 mg PO QID (n=47)
  - similar reduction in TSS between domperidone and metoclopramide: 41% vs. 39%
  - TSS = sum of four investigator-assessed scores ranging from 0 to 3 for: nausea, vomiting, early satiety, and bloating/distension

†Patterson et al., 1999

## Efficacy: Gastrointestinal Conditions, *cont.*

3. Randomized, active-controlled, 8-week trial - pediatric diabetic gastroparesis (5 to 17 years of age)<sup>#</sup> (n=28)
  - treatment arms = domperidone 0.9 mg/kg daily (n=14) and cisapride 0.8 mg/kg daily (n=14)
  - lower median TSS with domperidone than cisapride: 3.1 vs 7.4
  - TSS = sum of four investigator-assessed scores ranging from 0 to 6 for: regurgitation (or vomiting or heartburn), feeling of abdominal fullness (or bloating), early satiety or anorexia, and abdominal (epigastric and mesogastric) pain

<sup>#</sup>Franzese et al., 2002

## Efficacy: Gastrointestinal Conditions, *cont.*

- **Key limitations of gastroparesis trials:**
  - Trials 1-3:
    - Investigator assessment for the primary endpoint
    - Currently, patient-reported outcome (PRO) measures are recommended\*
  - Trial 2:
    - Reductions appeared similar (not stat. sig.)
    - But not a non-inferiority (NI) trial
      - A NI trial aims to show a novel treatment is not clinically worse than an active treatment based on a specific NI margin.

\*FDA Draft Guidance

## Efficacy: Gastrointestinal Conditions, *cont.*

- **Nausea and Vomiting:**
  - Currently approved outside of US for treatment of nausea and vomiting at a dose of 10 mg PO up to TID\*
  - Efficacy data mainly from 3 studies (each 4-week duration) in chronic postprandial dyspepsia<sup>#,†,§</sup> that together enrolled 251 and 249 patients receiving domperidone and placebo, respectively:
    - "...support the use of domperidone 10 mg tid in the suppression of nausea and vomiting symptoms at week 2 and/or week 4 of treatment"
    - "[c]linically relevant improvement in nausea and/or vomiting scores were reported in these studies following domperidone treatment compared to placebo"
  - Nausea and vomiting each assessed on a 4-point scale

<sup>#</sup> De Loose, 1980; <sup>†</sup>Englert et al., 1979; <sup>§</sup>Von Matushka, 1979

\* EMA PRAC Assessment Report, 2014

## Efficacy: Gastrointestinal Conditions, *cont.*

- **Alternative Approved Therapies**
  - Gastroparesis
    - One FDA-approved therapy - metoclopramide
      - Shown to be effective in treating gastroparesis
      - Boxed warning for tardive dyskinesia, a serious movement disorder that is often irreversible
  - Nausea and Vomiting
    - multiple FDA-approved therapies
      - Shown to be effective in preventing/treating nausea and vomiting

## Efficacy: Gastrointestinal Conditions, *cont.*

- **Efficacy Conclusions**

- Data from randomized controlled trials suggest efficacy for gastroparesis & nausea/vomiting.
  - Gastroparesis: Trials were either small or suffered from significant design limitations
  - Nausea/Vomiting: Trials were in the chronic postprandial dyspepsia population
- There is one FDA-approved therapy for gastroparesis and numerous FDA approved therapies for nausea/vomiting.



## Efficacy: Lactation Disorders

- Controlled studies: domperidone 30 mg daily (Cochrane review, Donovan et al, 2012):
  - Two randomized, placebo-controlled trials
  - Total of 59 mothers of preterm infants
  - Modest placebo-corrected increase in expressed breast milk of approximately 99 mL/day (95% CI: -2 to 201 mL) (~3.4 ounces) with domperidone 10 mg orally three times daily for 7 to 14 days
  - No significant improvements in longer-term outcomes of breastfeeding

Donovan TJ, Buchanan K. Cochrane Database Syst Rev. 2012; 14:3.

(Campbell-Yeo, M. L., et al Pediatrics, 2010;125(1), e107-114. da Silva, O. P., et al. CMAJ 2001;164(1), 17-21.)

## Efficacy: Lactation Disorders, *cont.*

- Uncontrolled studies: domperidone 30-60 mg daily
  - Increases prolactin levels to 150%-600% of baseline, within 15-45 minutes, in nonpregnant and lactating women
  - Increases milk production by 1.5-2 times baseline in lactating women (60 mg not more effective than 30 mg)
    - Studies were mostly observational, uncontrolled with short duration of follow-up
- **Efficacy Conclusions**
  - Scant reliable clinical data to support the drug's effectiveness or dosing recommendations for lactation disorders
  - No approved pharmacotherapies for lactation disorders

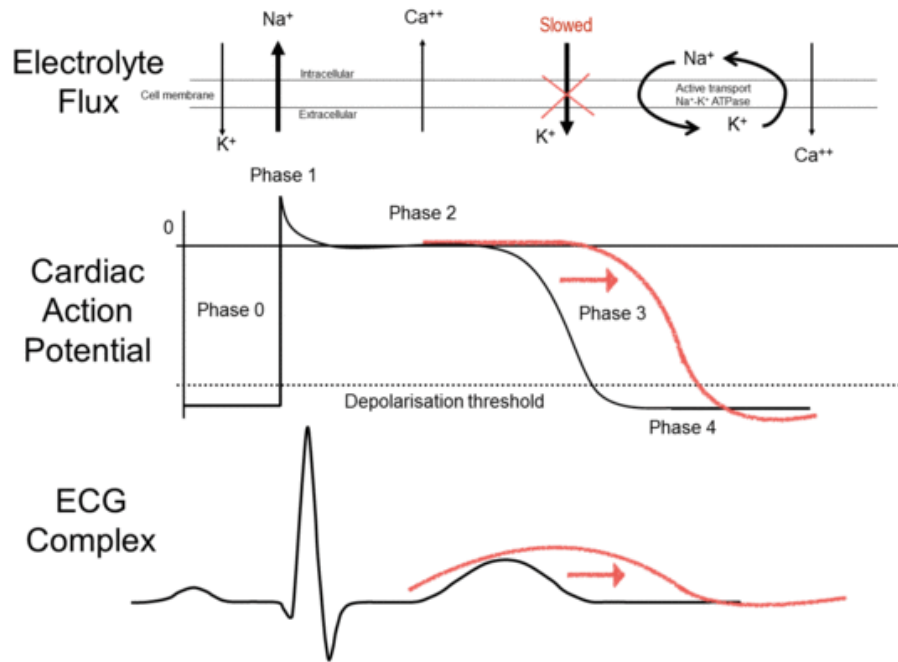
Brouwers, J. R., et al. *Clin Endocrinol.(Oxf)*, 12(5), 435-440. Wan, E. W., et al. *Br J Clin Pharmacol*, 66(2), 283-289.  
Knoppert, D. C., et al. *J Hum Lact*, 29(1), 38-44. doi: 10.1177/0890334412438961. Wagner, C.L., et al. *Breastfeeding Medicine*, 6.  
Camanni, F., et al. *Neuroendocrinology*, 30(1), 2-6. Ingram, J., et al. *Arch Dis Child Fetal Neonatal Ed*, 97(4), F241-245.  
doi:10.1136/archdischild-2011-300601. Campbell-Yeo, M. L., et al. *Pediatrics*, 125(1), e107-114. doi: peds.2008-3441 [pii]  
10.1542/peds.2008-3441. da Silva, O. P., et al. *CMAJ*, 164(1), 17-21.



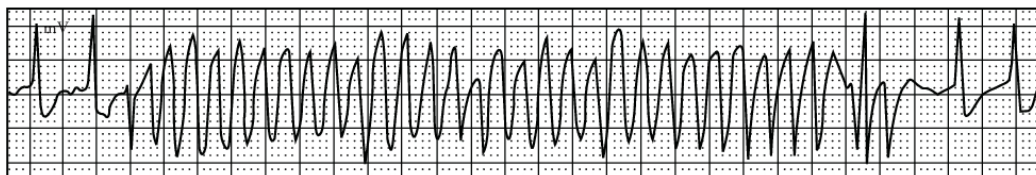
# Major Safety Concerns with Domperidone

**QT Interval Prolongation, Torsades de Pointes,  
Ventricular Arrhythmias, Sudden Death**

# QT Basics: Drug-Induced QT Interval Prolongation can lead to Torsades de Pointes (TdP)



**ECG Indicating Torsades de Pointes**



**Drug blocks potassium ion channel (Kv 11.1 / hERG) and reduces potassium current**

**Prolonged cardiac action potential duration (delayed repolarization phase)**

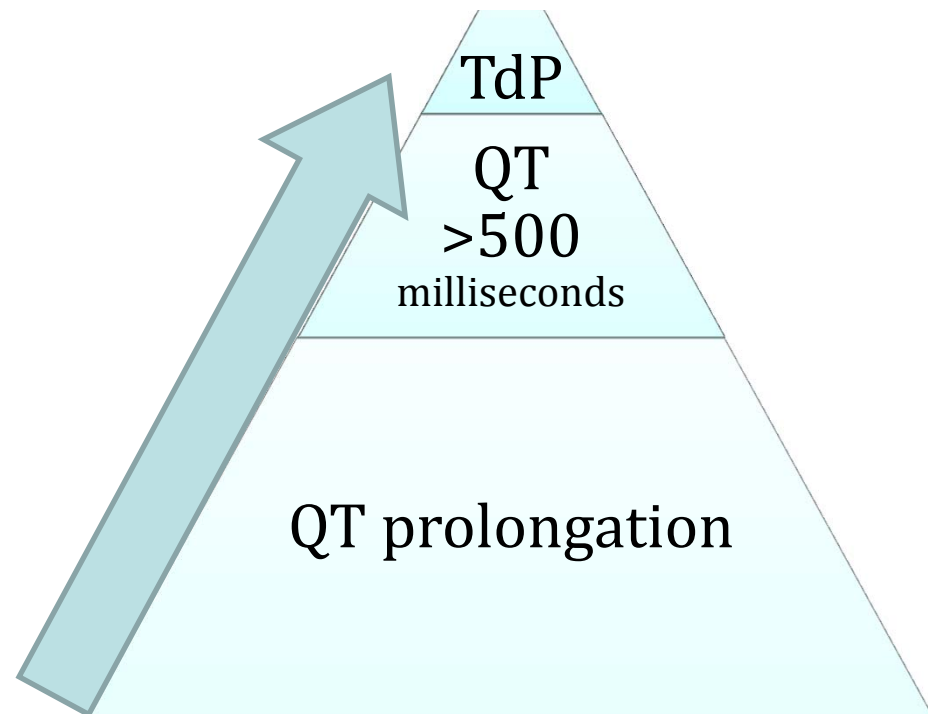
**Prolonged QT interval on ECG**

**An early after-depolarization beat can trigger arrhythmia**

<http://curriculum.toxicology/>

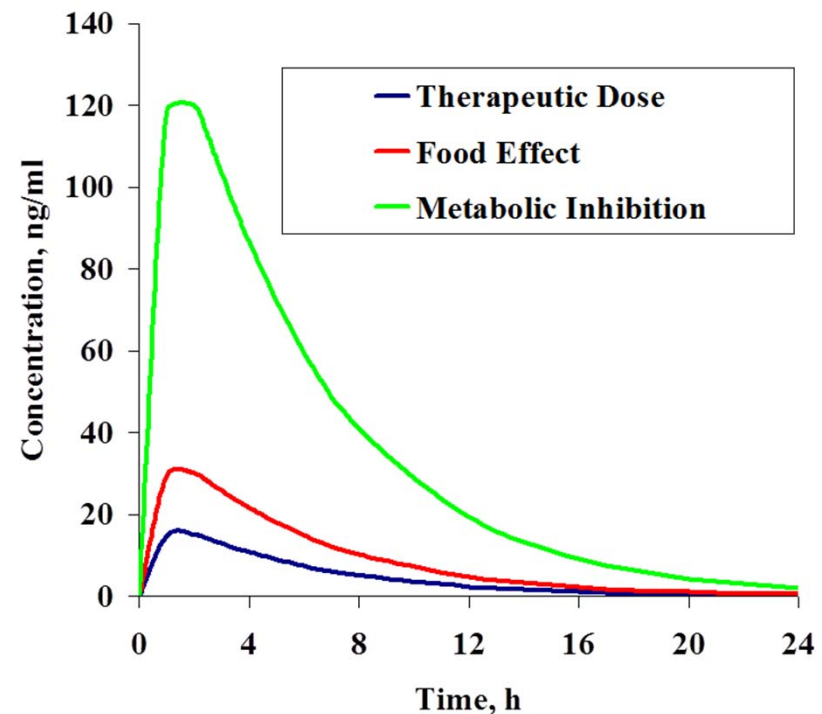
## QT Basics: Patient Risk Factors for Drug-Induced TdP

- Female sex
- Electrolyte abnormalities (hypokalemia, hypomagnesemia)
- Concomitant use of QT-prolonging drug
- High drug concentrations
- Bradycardia
- Baseline QT prolongation
- Subclinical long-QT syndrome
- Ion channel polymorphisms



# QT Basics: ICH E14 Guidance and Thorough QT Study

- Determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation,
  - Regulatory threshold is around **5 ms** as evidenced by an upper bound of the **95% CI around the mean effect of 10 ms**
- Randomized, blinded, positive- and placebo-controlled study in healthy subjects
  - Investigational drug is given at supratherapeutic doses

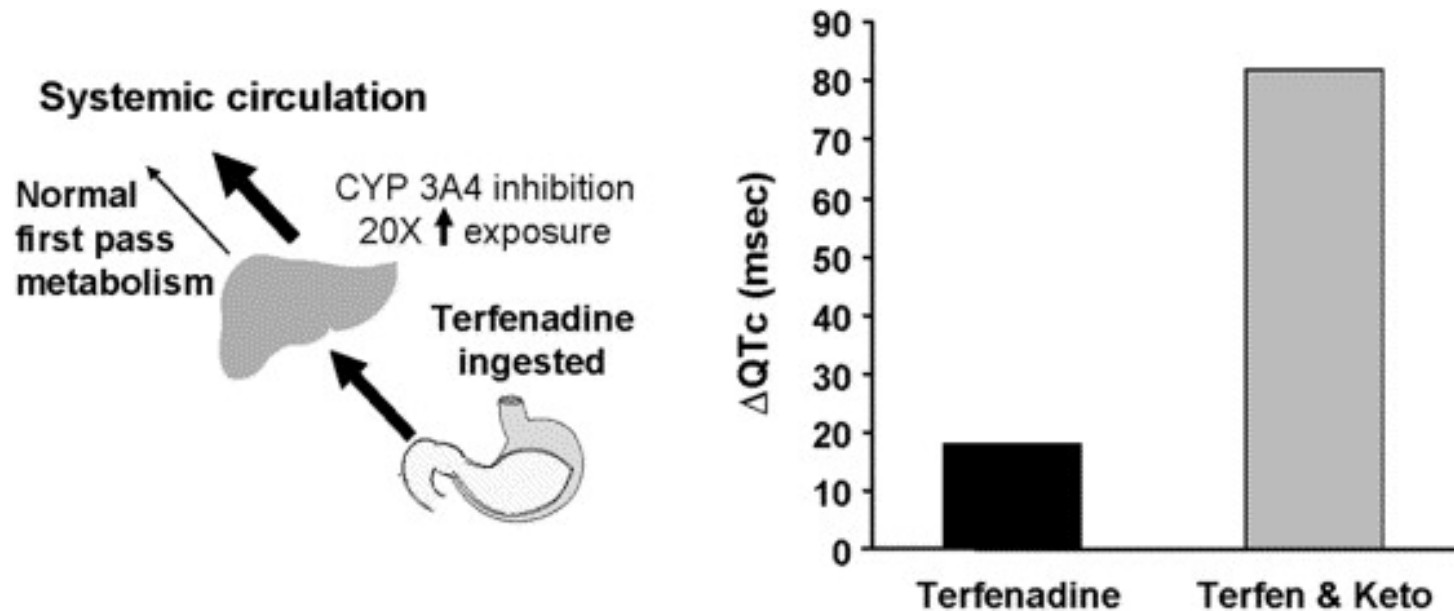


Supratherapeutic doses are expected to cover the high clinical exposure scenario in patients

## QT Basics: Drugs Withdrawn from U.S. Market due to QT Prolongation/TdP

Drug	Year of Introduction	Therapeutic Class	Year of Withdrawal
Prenylamine	1960s	Antianginal	1988
Terodiline	1986	Antianginal	1991
Terfenadine	1982	Antihistamine	1998
Astemizole	1986	Antipsychotic	1998
Grepafloxacin	1997	Antibiotic	1999
Cisapride	1988	Gastric prokinetic	2000
Levacetylmethadol	1997	Methadone substitution	2001
Propoxyphene	1960s	Opioid analgesic	2009

# QT Basics: Cardiac Safety and Marketing Withdrawal: Terfenadine



Mechanism
<ul style="list-style-type: none"> <li>• IKr blockade as mechanism for drug-induced QT prolongation and TdP</li> </ul>

Drug Interactions
<ul style="list-style-type: none"> <li>• Interaction of drugs can cause serious adverse events</li> <li>• PK variability important for safety assessment</li> </ul>

Benefit-Risk
<ul style="list-style-type: none"> <li>• Small risk of drug-induced TdP outweighed the benefit of reduction of symptoms</li> </ul>

Figure from Heist EK, Ruskin JN *Heart Rhythm*, 2005; 2(11): S1-S8



## Summary of QT Basics

- Drug-induced QT interval prolongation can lead to torsades de pointes, a potentially life-threatening arrhythmia.
- Thorough QT study determines whether a drug has a pharmacologic effect on cardiac repolarization at the doses and exposures evaluated in the study.
  - Importantly, drug is evaluated at supratherapeutic doses to cover the high drug exposure scenario in patients
- Risk of torsades de pointes is influenced by patient risk factors.



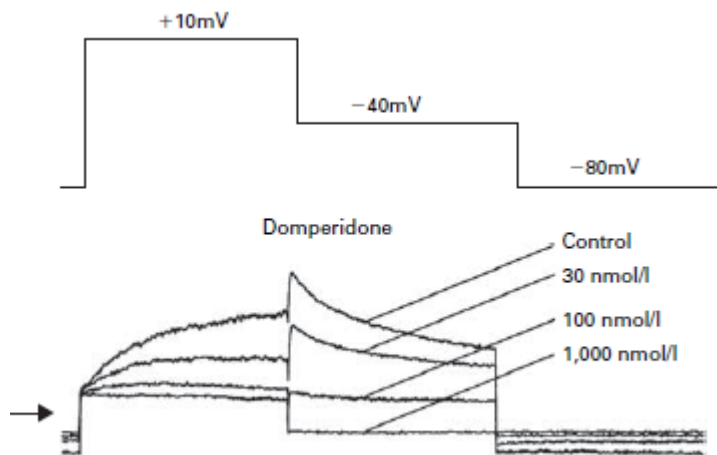
# Proarrhythmic Risk of Domperidone

# Nonclinical Assessment

## Toxicity of Domperidone: Disruption of Heart Rhythm

**Domperidone potently blocks cardiac potassium current**

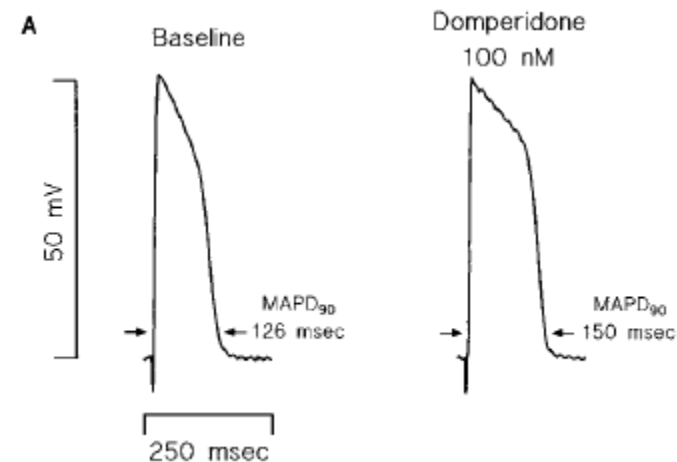
Kv11.1/hERG channel test\*



50% block at 57 nM  
Complete block at 1 uM

Claassen and Zunkler. 2005. Comparison of the Effects of Metoclopramide and Domperidone on HERG Channels. *Pharmacology* 74:31

**Domperidone prolongs the cardiac action potential at very low concentration**



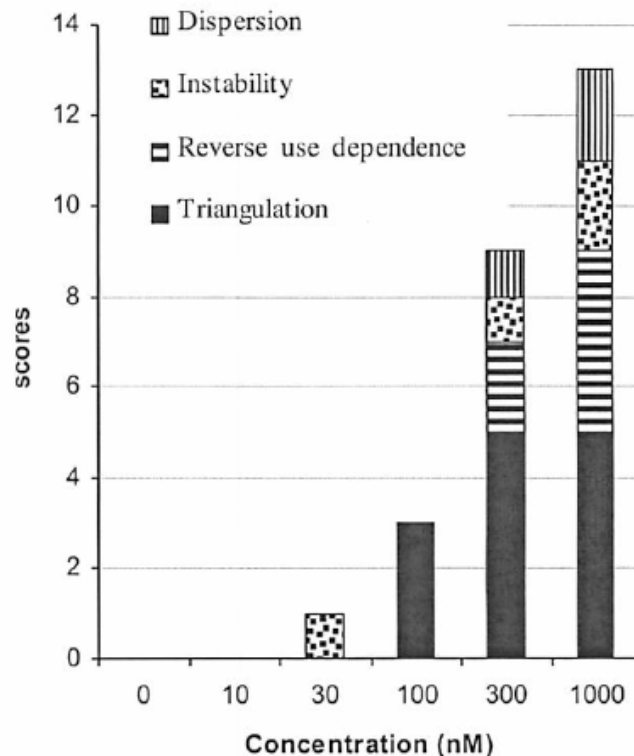
100 nM domperidone increased action potential duration by 24 msec in guinea pig heart\*

Drolet et al., 2000. Domperidone Should Not Be Considered a No-Risk Alternative to Cisapride in the Treatment of Gastrointestinal Motility Disorders. *Circulation* 102:1883.

# Nonclinical Assessment

## Toxicity of Domperidone: Disruption of Heart Rhythm, *cont.*

### TRiAD test\*



### Conclusions: Domperidone

- Blocks cardiac potassium channels
- Prolongs action potential duration
- Alters stability of the heart rate
- The above cardiac proarrhythmic effects occur at very low concentrations of domperidone (nM) in nonclinical assays

Hondegehm, 2011. Low safety index of domperidone: mechanism for increased odds ration for sudden cardiac death. Acta Cardiol 66(4):421.

## Thorough QT Study: Negative Findings

- Randomized, double-blind, 4-way crossover, placebo and positive-controlled, single- and multiple-dose study in 44 healthy adults
- Assessed the effects of domperidone on the QTc interval at the then-approved domperidone doses of 10 mg orally four times daily (qid) and 20 mg orally qid
  - non-supratherapeutic doses/exposures
- Showed no clinically relevant effect of domperidone on QTc interval at doses/exposures evaluated

European Medicines Agency: Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report: March 6, 2014.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referrals\\_document/Domperidone\\_31/Recommendation\\_provided\\_by\\_Pharmacovigilance\\_Risk\\_Assessment\\_Committee/WC500168926.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Domperidone_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500168926.pdf).

## Thorough QT Study, *cont.*

### Major study limitations

- Did not assess exposure in anticipated “worst case scenario” to predict QT safety in real world settings (e.g., concomitant administration with interacting drugs and other products; medical conditions that either contribute to QT prolongation or increase domperidone exposure)
- EMA’s explanation for not assessing greater exposure: “the inclusion of suprathreshold doses (administered in healthy volunteers) was ethically questionable, because a potential relevant QTc prolongation was foreseen.”

## Early Reports of Cardiotoxicity with Intravenous Domperidone

- Early 1980s: Reports of 7 patients with serious cardiac adverse reactions, including QT prolongation, torsade de pointes (TdP), cardiac arrest and sudden death with rapid infusion of intravenous domperidone for anti-nausea treatment during chemotherapy in cancer patients
  - Increasing number of such cases worldwide led to withdrawal of IV formulation in 1985
- These serious cardiac reactions subsequently noted with other pharmaceutical forms of domperidone, specifically oral and rectal suppository formulations

Joss, R. A. et al. Lancet 1982;1(8279): 1019. Giaccone, G, et al. Lancet 1984; 2(8415): 1336-1337. doi: S0140-6736(84)90841-9 [pii]. Bruera, E., et al. Cancer Treat Rep, 1986; 70(4), 545-546.

# Pharmacovigilance: Outside the U.S.

## Cases of QT Prolongation, Arrhythmias, Deaths With Oral, Rectal Formulations of Domperidone

### 2013 EMA report (oral, rectal formulations approved outside the U.S.):

- Sponsor's safety database (as of 2012): 342 cases of serious cardiac AEs were reported
  - Cardiac arrest (n=50), MI (n=41), EKG QT prolonged (n=39), Tachycardia (n=27)
  - 87 fatal cases: 64% female; 41% were  $\geq 65$  yo; dose commonly > 30 mg daily
  - 156 cases of cardiac conduction events
    - 60 cases with time to onset: 20 occurred the same day as the first dose, and in another 24 cases, the event occurred within that first week
- EMA's pharmacovigilance database (as of 2013): 219 cases
  - Ventricular arrhythmias and cardiac arrest (N=64), rate and rhythm disorder (N=60)
  - Median time to onset 2 days (range 0-1,135 days)
  - Risks increased in patients > 60 years of age, higher doses (> 30 mg orally daily) concomitant use of QT-prolonging drugs or products that increase domperidone exposure

European Medicines Agency: Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report: March 6, 2014.

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referrals\\_document/Domperidone\\_31/Recommendation\\_provided\\_by\\_Pharmacovigilance\\_Risk\\_Assessment\\_Committee/WC500168926.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Domperidone_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500168926.pdf).



# Pharmacovigilance: FAERS

## (FDA Adverse Event Reporting System)

- Strengths
  - Includes US and may include foreign drugs, all uses
  - Especially good for detecting rare, serious adverse events
  - Useful for detecting events that occur shortly after exposure
  - Detection of events not seen in clinical trials
- Limitations
  - Passive surveillance: underreporting
  - Cannot determine incidence
  - Quality of information in report variable

Major limitation with domperidone: Because domperidone is an unapproved drug, there is a high likelihood of underreporting of adverse events

# Pharmacovigilance: FAERS

## Cases of QT Prolongation, Arrhythmias, Deaths With Oral Domperidone

### FAERS search in females $\leq$ 50 years old taking oral domperidone (January 1, 1965. April 16, 2015)

- Some illustrative case reports without other risks for cardiac arrhythmias:
  - 2013 (USA) : After 4 days of domperidone 20 mg daily, a 46-year-old female with long-standing GERD, experienced torsade de pointes during the stress test; cardioversion was unsuccessful, and patient died.
  - 2012 (USA) : After 4 days of domperidone 120 mg daily for lactation enhancement, a 34-year-old woman had palpitations, shortness of breath, and difficulty getting out of bed. EKG showed QT prolongation, which resolved after drug discontinuation.

# Pharmacovigilance: FAERS

## Cases of QT Prolongation, Arrhythmias, Deaths

### With Oral Domperidone, *cont.*

#### FAERS data *cont'd*:

Some illustrative case reports with patient risks for cardiac arrhythmias:

- 2013 (Great Britain): a 34-year-old female treated with oral domperidone 30 mg daily collapsed and had complete heart block.  
Patient risks: concomitant medications sumatriptan, sertraline, and ondansetron
- 2012 (Canada): 19-year-old female had QT prolongation on oral domperidone (?dose), ciprofloxacin and metronidazole. She also had hypokalemia and borderline hypomagnesemia. Symptoms resolved with drug discontinuation and electrolyte repletion.  
Patient risks: concomitant medication ciprofloxacin, electrolyte abnormalities
- 2006 (USA): 35-year-old healthy woman was treated with oral domperidone (?) for lactation enhancement. She developed QT prolongation and syncope 2 days after adding azithromycin to her medication regimen. No further outcomes reported.  
Patient risk: Concomitant azithromycin

# Pharmacoepidemiological Studies: Increased Risk of Sudden Cardiac Death/Serious Ventricular Arrhythmia With Domperidone Use

## FDA literature review:

- Systematic literature search yielded 15 articles from six interpretable non-experimental (clinical or non-clinical) studies of domperidone and QT interval prolongation, torsade de pointe, serious ventricular arrhythmia, or sudden cardiac death
  - Evidence for a **1.5- to 2.0-fold risk** of sudden cardiac death (SCD) from current use of domperidone in the general population
  - EMA's pharmacoepidemiologic review included many of the same studies; similarly concluded that domperidone exposure was associated with an increased risk ratio for SCD and/or SVA.
  - No data to inform differences in risks in breastfeeding women

## Limitations of studies:

- Residual confounding, exposure misclassification, and protopathic bias\*

\*A type of bias that can occur if the first symptoms of the outcome of interest are the reasons for using the treatment under study” from Porta, M, 2008, A Dictionary of Epidemiology, Oxford, Oxford University Press, page 198

# Pharmacoepidemiological Studies: Increased Risk of Sudden Cardiac Death/Serious Ventricular Arrhythmia With Domperidone Use, *cont.*

- Johannes et al, 2010: population-based, nested case-control study using electronic databases of Saskatchewan Health
  - 1,559 cases of SCD and 49 cases of serious ventricular arrhythmia (SVA); 6,428 matched controls (non-cases)
  - Mean age of cases and controls 79 years; over 50% female
  - Adjusted odds ratio (OR) for the composite endpoint SCD/SVA associated with current domperidone use was 1.59 (95% CI 1.28-1.98)
  - **Conclusion:** Findings suggests that current domperidone use was associated with a **1.6-fold increase** in the risk of for the composite endpoint of SVA/SCD

Johannes, C. B., et al Pharmacoepidemiol Drug Saf, 2010; 19(9),881-888.

## Pharmacoepidemiological Studies: Increased Risk of Sudden Cardiac Death/Serious Ventricular Arrhythmia With Domperidone Use, *cont.*

- Van Noord et al, 2010: population-based, case-control study using Netherlands Integrated Primary Care Information database
  - 1,304 cases of SCD and 62 of SVA; 14,114 matched controls
  - Mean age of SCD cases 72.5 years; 42% women
  - Adjusted odds ratio was 1.92 (95% CI 0.78-4.73) for the composite endpoint of SCD/ SVA, and 1.99 (95% CI 0.80-4.96) for the endpoint SCD
  - **Conclusion:** Findings suggest that domperidone use was associated with an approximate **2-fold increase** in the risks of SCD and SVA.

# Drug-Drug Interaction Studies: QT Interval Prolongation

- Domperidone 10 mg 4 times/day combined with a strong or moderate CYP3A4 inhibitor that also prolongs QT interval (ketoconazole and erythromycin used in these two studies):
  - A 2- to 3-fold increase in domperidone blood concentrations (C<sub>max</sub>)
  - Statistically significant increase in QT<sub>cF</sub> compared to placebo was observed at most timepoints during the 24-hour observation period:
    - Maximal mean increase of 13.6 to 15.3 msec when domperidone was administered in combination with ketoconazole or erythromycin
    - Exceeds the ICH-E14 guideline's regulatory threshold of concern for the QT<sub>c</sub> interval prolongation (a max mean increase in QT<sub>c</sub> interval of >5 msec with an upper bound 95% confidence interval of >10 msec, compared to placebo)

## Drug Interactions: Multiple Drug Classes That Interact With Domperidone

- **Drugs in the following classes**
  - Antidepressants
  - Antilipemics
  - Anti-psychotics
  - Hematological Agents
  - Anti-Emetics
  - Respiratory Agents
  - Anti-infective agents
  - Gastrointestinal Agents
  - Anti-Fungal Agents
  - Antidiarrheal
  - Antivirals
  - Antihistamines
  - Protease Inhibitors
  - Migraine treatment
  - Anti-Hypertensives
  - Antimalarial
  - Calcium Channel Blockers
  - Muscle relaxants
  - Anti-Arrhythmics
  - Other
  - Diuretics
- **See full listing in the Briefing Document**



# Drug Interactions: Multiple Drugs That Interact With Domperidone, *cont.*

1. Antidepressants: doxepin (Adapin®, Sinequan®, Zonalon®), clomipramine (Anafril®), amoxapine (Asendin®), trazodone (Desyrel®), venlafaxine (Effexor®), nefazodone (Serzone®), fluvoxamine (Luvox®), paroxetine (Paxil®), fluoxetine (Prozac®, Sarafem®), sertraline (Zoloft®), amitriptyline (Elavil®, Endep®, Etrafon®, Limbitrol®, Triavil®), maprotiline (Ludiomil®), desipramine (Norpramin®), nortriptyline (Pamelor®), trimipramine (Surmontil®), imipramine (Tofranil®), protriptyline (Vivactil®),
2. Anti-psychotics: haloperidol (Haldol®), chlorpromazine (Thorazine®, Ormazine®), chlorpromazine pamoate (Orap®), sertindole (Serlect®), quetiapine (Seroquel®), mesoridazine (Serentil®), perphenazine (Triavil®), fluphenazine (Apo-Fluphenazine®), Modecate Concentrate®, Moditen®, Permitil®, PMS-Fluphenazine®, Prolixin®, Rho-Fluphenazine®, promazine (Sparine®), trifluoperazine (Stelazine®)
3. Anti-Emetics: prochlorperazine (Compazine®), thioridazine (Mellaril®), promethazine (Phenergan®), mesoridazine (Serentil®), thiethylperazine, (Torecan®), perphazine (Trilafon®), dolasetron (Anzemet®), dronabinol (Marinol®), droperidol (Inapsine®)
4. Anti-infective agents: erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin®, Pediazole®, Aknemycin®), clarithromycin (Biaxin®), troleandomycin (TAO®), norfloxacin (Chibroxin®, Noroxin®), quinine sulfate, quinupristin and dalfopristin (Synercid®), pentamidine (Nebupent®, Pentacarinat®, Pentam®), sparfloxacin (Zagam®), grepafloxacin (Raxar®), azithromycin (Zithromax®), ofloxacin (Floxin®) levofloxacin (Levaquin®)
5. Anti-Fungal Agents: fluconazole (Diflucan®), itraconazole (Sporanox®), ketoconazole (Nizoral®), miconazole (Micatin®, Monistat®), terconazole (Terazol®), ticonazole (Vagistat®), butaconazole (Femstat 3®)
6. Antivirals: foscarnet (Foscavir®)
7. Protease Inhibitors: indinavir (Crixivan®), amprenavir (Agenerase®), ritonavir (Norvir®), nelfinavir (Viracept®), saquinavir (Invirase®, Fortovase®),

# Drug Interactions: Multiple Drugs That Interact With Domperidone, *cont.*

8. Anti-Hypertensives: nicardipine (Cardene®), isradipine (Dynacirc®), moexipril/HCTZ (Uniretic®)
9. Calcium Channel Blockers: verapamil (Calan®), diltiazam (Cardizem®), diltiazem/enalapril (Teczem®), verapamil/trandolapril (Tarka®), tocainide (Tonocard®), bepridil (Vascor®)
10. Anti-Arrhythmics: disopyramide (Norpace®, Norpace CR®), quinidine (such as Quinidex®, Cardioquin®, Quinaglute®, Duraquin®), procainamide (Procanbid®, Procan®, Pronestyl®), flecainide (Tambocor®), sotalol (Betapace®), bretylium (Bretylol®), amiodarone (Cordarone®), ibutilide (Corvert®), moricizine (Ethmozine®)
11. Diuretics: bumetanide (Bumex®), furosemide (Lasix®), torsemide (Demadex®), ethacrynic Acid (Edecrin®), chlorothiazide (Diuril®), Indapamide (Lozol®)
12. Antilipemics: Bepridil (Vascor®), mibefradil (Posicor®)
13. Hematological Agents: cilostazol (Pletal®)
14. Respiratory Agents: zafirlukast (Accolate®), salmetrol (Serevent®)
15. Gastrointestinal Agents: cimetidine (Tagamet®), cisapride (Propulsid®)
16. Antidiarrheal: octreotide (Sandostatin®)
17. Antihistamines: azelastine (Astelin®), clemastine (Tavist®)
18. Migraine treatment: naratriptan (Amerge®), sumatriptan (Imitrex®), zolmitriptan (Zomig®)
19. Antimalarial: halofantrine
20. Muscle relaxants: tizanidine (Zanaflex®)
21. Miscellaneous: tamoxifen (Nolvadex®), warfarin (Coumadin®), phenytoin (Dilantin®), ziprasidone (Geodon®), risperidone (Risperdal®), formoterol fumarate (Foradil Aerolizer®), sildenafil (Viagra®)

## Other Safety Considerations: Pediatric Population

- Several studies published between 2005 and 2013 reported QT prolongation in infants treated with domperidone for various gastrointestinal indications
  - Doses reported in three of the studies ranged from 1.0 to 2.1 mg/kg/day in divided doses
  - One study showed the QT prolongation was not related to the dose of the drug
  - Another report was related to an accidental overdose given at home, 50 mg in 4 hours

Günlemez A, et al. *J Perinatol* 2012; 30:50-53. Vieira MC, et al. *Acta Pædiatrica* 2012; 101:494-496.  
Djeddi, et al. *J Pediatr* 2008;153:663-666. Rocha CMG, et al. *Pediatr Cardiol* 2005; 26:720-723.  
Sanklecha et al. *Indian J Pediatr* 2013; 80(7):615.

## Other Safety Considerations: Domperidone Exposure To Breastfed Infants Via Breast Milk

- Domperidone is transferred into human breast milk:
  - Maternal doses of 10 mg, three times daily results in breast milk concentrations of 1.2 ng/mL. Assuming a daily milk intake of 150 mL/kg, this would result in a calculated dose of <0.2 mg/kg/day ingested by the infant
  - Maternal doses of 10 mg and 20 mg, orally, three times daily results in calculated infant doses of 0.03-0.07 mcg/kg/d and 0.05-0.11 mcg/kg/day, assuming a daily milk intake of 150 mL/kg

Hofmeyr GJ. Br J Obstet Gynaecol.1985;92:141-144. Wan, E. W., et al. Br.J Clin Pharmacol.2008;66(2), 283-289. da Silva, O. P., 2001;CMAJ, 164(1), 17-21.

# Safety Conclusions

- Domperidone is associated with serious risks of QT prolongation, ventricular arrhythmias and sudden cardiac death.
- Cases of cardiotoxicity have been reported with domperidone, in intravenous, rectal, and oral formulations.
- Patients with cardiotoxicity often have cardiovascular risks, concomitant medications, and other risk factors for QT prolongation. These cases reflect real-world cardiac safety of domperidone.
- Serious adverse cardiac arrhythmias have also occurred in otherwise healthy young women with no apparent risk factors.

## Safety Conclusions, *cont.*

- Domperidone prolongs the QT interval, but the dose- and exposure-response is not well characterized:
  - QT prolongation, cardiac arrhythmias, and sudden death reported with doses of domperidone approved in jurisdictions outside of the US
  - Lack of assessment of suprathreshold exposures (reflective of real-world scenarios) in the thorough QT study does not inform the risk threshold of QT prolongation with real world use of domperidone
  - Domperidone is susceptible to drug interactions with drugs that increase domperidone exposure/also prolong QT interval
- Domperidone is secreted in human breast milk, which poses unknown risks to the exposed infant.

## Safety Conclusions, *cont.*

- Given the safety concerns, there is potential for significant harm to the public if domperidone is prescribed and used without important safeguards to ensure adequate patient protection

### Examples of safeguards

- assessment of risk factors and medications that could increase risk of QT prolongation
- appropriate dose and dose regimen
- proper patient selection
- patient monitoring

## Regulatory History – Outside the U.S.

- 1978: Initial approval of domperidone in Europe for certain GI conditions
- 1985: IV formulation withdrawn worldwide due to reports of QT prolongation, ventricular arrhythmias, and sudden death
- 2014: EMA recommended:
  - Restricting indication to treatment of nausea and vomiting only
  - Maximum dose reduced to 30 mg daily, up to maximum duration 7 days for adults and adolescents weighing 35 kg or more
  - Withdrawal of higher-dose oral, rectal formulations
  - New contraindications
- 2014: “Non-prescription” status revoked in Belgium, Netherlands, and UK; access now is by prescription only
- 2015: Health Canada recommended:
  - Health Care Professional Warning, Public Communication Warning, Recalls & Alert Advisory to warn of serious ventricular arrhythmias and sudden cardiac death; same recommendations as the EMA



# Regulatory History – U.S.

## 2004: Import Alert, Safety Alert

- Potential cardiac toxicity of domperidone, including QT interval prolongation
  - \* Post-market adverse events of cardiotoxicity, including QT prolongation and cardiac arrhythmias reported in non-U.S. markets
- Secretion of the drug in breast milk (unknown: absorption and infant exposure, safety risk to lactating mother and breastfeeding infants)

# Regulatory History – U.S., *cont.*

## Warning Breast-Feeding Mothers about Domperidone

FDA Patient Safety News: Show #30, August 2004

Here's a warning to pass on to patients who are breastfeeding their babies. FDA has received numerous reports of pharmacies compounding the drug domperidone and of lactating women using the drug to try to increase their milk production.

Domperidone isn't approved for that indication, and in fact it's not approved for any indication in this country. It's also not approved in any country for increasing breast milk production. (It's been approved in several foreign countries, but only to treat certain gastric disorders.)

U.S. women using domperidone have been buying it from compounding pharmacies in this country, and also online from sources outside the U.S.

FDA is concerned that women may be risking their health if they use domperidone to try to increase milk production. There are reports of cardiac arrhythmias, cardiac arrest and sudden death in patients receiving an IV form of the drug, and in fact that form is no longer marketed.

At high oral doses, seizures and other neurologic side effects have been reported, and those are the doses that have been suggested for breastfeeding women. In addition, using certain other drugs, such as erythromycin, could raise blood levels of domperidone even further and increase the possibility of serious adverse effects. In several countries where the oral form of domperidone is marketed, the drug's labeling specifically warns that nursing mothers should not use it.

Using domperidone may place the infant at risk, too. That's reflected in the labeling in many countries where the drug is approved for other purposes. The labeling notes that the drug is excreted in breast milk, and that could expose a breastfeeding infant to unknown risks.

The bottom line is to advise patients who are breastfeeding not to use domperidone to try to increase their milk supply.

### **Additional Information:**

FDA Talk Paper: FDA Warns Against Women Using Unapproved Drug, Domperidone, to Increase Milk Production.

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm>

## Regulatory History – U.S., *cont.*

- No pharmacies are allowed to compound domperidone.
- Since 2004: FDA has issued multiple warning letters to pharmacies that compound products containing domperidone and firms that supply domperidone for use in compounding.

## Regulatory History – U.S., *cont.*

- Domperidone available through IND Expanded Access Program
  - Dougherty's Pharmacy in Dallas, TX, is currently the only pharmacy authorized to dispense manufactured domperidone
  - Authorized manufacturers: Idis House (United Kingdom) and Pharmascience (Canada)
- IND Expanded Access Protocol
  - Refractory GERD with upper GI symptoms, gastroparesis, chronic constipation in patients  $\geq 12$  years of age
  - Exclusion criteria: clinically significant bradycardia, sinus node dysfunction, heart block, prolonged QTc, history of ventricular tachycardia, ventricular fibrillation
  - Dose regimen: 10-30mg 4x/day
  - **Contains important protections of patients:** Informed consent, scheduled cardiovascular monitoring, list of drugs that interact with domperidone

## Overall Conclusions

- Efficacy and appropriate dosing regimen for domperidone as a galactagogue are uncertain. Given the serious proarrhythmic risks reported, the use of domperidone in the compounding setting for this indication is unacceptable.

## Overall Conclusions, *cont.*

- Evidence of efficacy of domperidone for nausea/vomiting and gastroparesis is not robust. Given the serious proarrhythmic risks reported and the availability of FDA-approved products to treat these conditions, use of domperidone for GI conditions in the compounding setting is also unacceptable.
  - In the US, domperidone is available for the treatment of GI conditions under the Expanded Access IND program, ensuring a specified dose range, appropriate patient selection, exclusion of factors that increase the risk of QT interval prolongation, informed consent, and adequate safety monitoring

## Final Recommendation

We **do not** recommend that domperidone, at any dose, be placed on the list of bulk substances that can be used to compound under section 503A of the FD&C Act.