Dimercapto-1-propanesulfonic Acid (DMPS)

Pharmacy Compounding Advisory Committee Meeting

June 23, 2016

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)
DMPS
Review Team

George Shashaty, MD, Medical Officer, DHP/OHOP
Kathy Robie Suh, MD, PhD, Clinical Team Leader, DHP/OHOP
Brenda J. Gehrke, PhD, Pharmacologist, DHOT/OHOP
David Lewis, PhD, Chemist, DPMAI, OLDP, OPQ
Ann Farrell, MD, Director, DHP/OHOP
Norman R. Schmuff, PhD, Associate Director for Science, OPF
Christopher M. Sheth, PhD, Team Leader, DHOT/OHOP
John K. Leighton, PhD, DABT, Division Director, DHOT/OHOP
DMPS: Nomination

• Use: “for treatment of heavy metal poisoning.”

• Route of administration: Oral, Intravenous injection, intramuscular injection.

• Materials received
  – Publications of anecdotal reports and mostly uncontrolled series of cases of exposure to various heavy metals treated with DMPS.
DMPS: Chemistry*

- Most commonly supplied as its sodium salt.
- Non-hygroscopic, exists as monohydrate.
- MW-228.3 Daltons.
- Stable in the crystalline form.
- Relatively stable in aqueous solutions, but labile to oxidation.

* Information based on Heyl Scientific Product Monograph
DMPS: Chemistry (cont) *

- Purified by release from the lead salt.
- Potential in process impurities: lead, allyl bromide, allyl sulfonic acid, and 2,3-dibromopropane-1-sulfonic acid.
- Potential heavy metal contamination can be monitored using USP compendial methods.

* Information based on Heyl Scientific Product Monograph.
DMPS: Nonclinical*

• Pharmacology
  – Mechanism of action not fully characterized.
  – Increases the urinary elimination of arsenic and interferes with arsenic methylation.
  – Promotes excretion and protects against mercury-induced renal damage by inhibiting mercury accumulation in renal proximal and distal tubular cells.

• Toxicokinetics
  – Oral absorption 30% in rats and 60% in dogs with peak plasma concentrations reached after 30 to 45 minutes.
  – Distribution after IV dose mainly into plasma and kidneys.
  – Elimination renal with a serum half-life of about 20 to 60 minutes.

* Based on April 2009 WHO document and Heyl monograph
DMPS: Nonclinical (cont)*

- Safety pharmacology
  - Relatively low acute toxicity; LD50 for parenteral administration approximately 1 to 2 g/kg.
  - Relatively low chronic toxicity in dogs and rats.
  - No evidence of adverse effects on cardiovascular, gastrointestinal, or renal systems.
  - No data available on central nervous system or respiratory system.
- Not mutagenic in the Ames test.
- No reproductive toxicity or teratogenicity shown in animals.
- Information on carcinogenicity is not available.

* Based on April 2009 WHO document and Heyl monograph.
DMPS Safety: Major Associated Adverse Reactions

• Serious case of Stevens-Johnson reported; one death due to severe diffuse desquamation.

• Dermatologic reactions, nausea and vomiting, hypotension, increases in serum transaminases, transient bronchospasm, fever, leukopenia.

• Reactions typically mild or moderate in severity.
DMPS: Clinical Evaluation of Effectiveness

• Uses in published studies and reports include for high arsenic in drinking water, lead poisoning, mercury poisoning, mercury excess from facial cream, mercury-containing dental amalgams, Wilson’s disease, high bismuth.

• Most reports are of uncontrolled use or anecdotal reports.

• Literature search found no adequate scientific studies that demonstrate the effectiveness of DMPS for the reported uses.
FDA Approved Drugs for Treatment of Heavy Metal Poisoning

- Multiple available approved drugs for treatment of heavy metal poisoning
  - Calcium disodium versenate (edetate disodium calcium) – lead.
  - Chemet (2,3,-dimercaptosuccinic acid; succimer; DMSA) – lead.
  - BAL (British Anti-Lewisite; dimercaprol) – arsenic, gold, mercury.
  - Cuprimine (penicillamine) – Wilson’s disease, cystinuria, severe active rheumatoid arthritis.
  - Syprine (trietine dihydrochloride) – Wilson’s disease (2nd line).
DMPS: Historical Use in Compounding

• Reported at 1998 PCAC that compounding dates to mid-1980s.
• Clinical use of DMPS mentioned in literature as early as 1958.
• Internet search suggests main “intended uses”
  – Treatment of persons with presumed mercury toxicity due to mercury amalgam dental fillings.
  – Treatment of persons with autistic disorders.
Conclusions

• DMPS is well defined and can be identified consistently, but manufacture may leave residual impurities, including lead which is toxic.

• Clinical investigation of use of the DMPS has been inadequate to establish safety.

• No clear evidence for clinical benefit of DMPS as currently used.
  – FDA-approved medications are available for treating heavy metal poisoning.

• Historical use dating to 1950s.
Recommendation

- We recommend that DMPS *not be included* on the list of bulk drug substances that can be used in compounding under section 503A of the Federal, Food, Drug, and Cosmetic Act.