Assessment 5: Since its first clinical report in 1980, SADBE has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence for current widespread use is not apparent.

V. Available Evidence of Effectiveness

Alopecia areata and warts frequently resolve without any therapeutic intervention. For example, in a study of the natural history of alopecia areata, of 63 alopecia areata patients followed for one year without treatment, hair had regrown in all but 4 patients in one year, and in all but 1 patient after two years. The great majority had recovered by 3 months after their only office visit (Arnold, 1952). Alopecia areata with less than 25% involvement has a high incidence of spontaneous recovery, whereas more severe involvement has a lesser rate of recovery (Moschella and Hurley, 1992). Regarding the natural history of warts, a two-year study showed that two-thirds of warts regressed without treatment (Massing and Epstein, 1963).

Despite the necessity for a placebo arm in evaluating experimental therapies such as SADBE, much of the excitement generated about topical immunomodulators stems from studies that were either uncontrolled or internally controlled. Describing therapy for alopecia areata, Rook et al. state: “The widely conflicting claims for the success of many different measures merely reflect the very great variations in the spontaneous course of the disease.”

Studies that demonstrate a “positive” result, such as regrowth of hair, is more likely to be submitted for publication or published than are studies with “negative” results. Therefore, the published literature may overstate the efficacy of novel therapies. Additionally, most clinical studies lack long-term follow-up, so the lasting treatment benefits cannot be evaluated.

Warts

Warts, caused by cutaneous infection with the human papillomavirus, are another very common dermatological ailment. Aside from cosmetic disfigurement, patients seek treatment for these lesions because plantar (foot) warts may cause pain on walking or interfere with gait, and warts on the fingers may interfere with manual dexterity. As with alopecia areata, therapy is not always effective, although the absence of a control arm precludes any definitive comparisons with other modalities.

<table>
<thead>
<tr>
<th>Table 2 - Use of SADBE in Human Papillomavirus Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
</tr>
<tr>
<td>Paller et al.</td>
</tr>
<tr>
<td>Iijima et al.</td>
</tr>
</tbody>
</table>
Alopecia areata

To make sense of the efficacy of the use of topical sensitizers for the treatment of alopecia areata, Naldi et al., 1990, reviewed 26 papers on "published clinical trials on dinitrochlorobenzene, squaric acid dibutylester, and diphenycyprone [DPCP] each published between January 1977 and January 1988." The authors of the paper stated, "According to our evaluation, the published literature is of limited use in defining the role of topical immunotherapy in alopecia areata. Half the studies examined used informal methods (uncontrolled or historically controlled trials)... In general, the studies we examined had serious drawbacks in reporting critical procedures such as assessing treatment and selecting and following up patients... In conclusion, a definite role of topical immunotherapy for alopecia areata has yet to be established and this treatment should be offered only as an experimental modality..." To date, there have been at least 14 reports in the peer-reviewed English-language literature on the use of SADBE for treatment of alopecia areata. Three of the most recent studies are presented in Table 3.

Table 3 - Use of SADBE in Alopecia Areata

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Disease</th>
<th>N</th>
<th>Treatment</th>
<th>Response/ITT</th>
<th>Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosti et al.</td>
<td>J. Am. Acad. Dermatol.</td>
<td>1996</td>
<td>Alopecia totalis in children</td>
<td>33</td>
<td>30.3% complete</td>
<td>70% relapse rate</td>
<td>No</td>
</tr>
<tr>
<td>Micali et al.</td>
<td>Int. J. Dermatol.</td>
<td>1996</td>
<td>Alopecia areata</td>
<td>144</td>
<td>64% with some regeneration</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Orecchia et al</td>
<td>Pediatr. Dermatol.</td>
<td>1994</td>
<td>Alopecia areata in children &lt;13 years</td>
<td>28</td>
<td>Weekly for 12 months</td>
<td>32.1% complete or acceptable 21.4% partial</td>
<td>No</td>
</tr>
</tbody>
</table>

More recently (in 1998) Rokhsar and his colleagues from the Department of Dermatology at N.Y.U. examined the efficacy of contact sensitizers in alopecia areata in a summary review of the literature. They present a more detailed study of the available literature on the use of SADBE to treat alopecia areata. Their overview of the data in the literature shows a response rate range from 29% to 87%. This includes a sum of both complete and partial responders. The weighted average response rate is 59%, which is similar to the response rate seen in the largest study by Micali et al. Interestingly, a relapse rate of 50-70% was seen in the patients even with continuation of treatment, suggesting that in many patients the response is temporary at best.

A tabular summary of the suggested role of immunomodulators (as gleaned from the leading dermatological textbooks) for the treatment of these disorders is presented in Table 4. There exist many therapeutic alternatives for alopecia areata and warts. The general consensus is that SADBE is currently a potentially useful experimental therapy for patients who fail more conventional therapy. It has shown a modicum of short-term efficacy, but additional well-controlled, long-term studies are needed to evaluate efficacy.

Assessment 6: Taking into account the available information, there is minimal evidence that SADBE is effective in the long-term treatment of alopecia areata or verruca.
Treatment of alopecia areata with SADBE may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.
### Table 4 - Perspectives on use of SADBE for Treatment of Alopecia Areata and for Warts

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease</th>
<th>Treatment of Choice</th>
<th>Other Suggested Treatments</th>
<th>Role of SADBE in Therapeutic Armamentarium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Andrews' Diseases of the Skin: Clinical Dermatology</strong>, ed. by Arnold et al., Eighth edition (1990) (textbook)</td>
<td>Alopecia Areata—patchy involvement</td>
<td>Intralional injections of corticosteroid</td>
<td>“None of the other various therapeutic approaches are clearly superior to corticosteroids”</td>
<td>SADBE: not discussed</td>
</tr>
<tr>
<td><strong>Dermatology in General Medicine</strong>, ed. by Fitzpatrick et al., Third edition (1987) (textbook)</td>
<td>Alopecia Areata—totalis/universal</td>
<td>Systemic (IM) steroids should be “seriously considered”</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common/Plantar Warts</td>
<td>Treatment of choice not identified</td>
<td>A, B, C, D, E, F, G, H, I, J, K (not plantar warts), L, M</td>
<td>“It (SADBE) may be worth trying in very large and resistant warts.”</td>
</tr>
<tr>
<td></td>
<td>Warts</td>
<td>Treatment of choice not identified</td>
<td>A, B, C, D, E, F, G, H, I, J, K, T, U, V</td>
<td>SADBE: may be suitable substitute, because it is negative in the Ames mutagenicity assay</td>
</tr>
<tr>
<td><strong>Pediatric Dermatology</strong>, ed. by Schachner and Hansen, (1988) (textbook)</td>
<td>Alopecia Areata</td>
<td>Treatment of choice not identified</td>
<td>O (unclear if regrowth is maintained), P (not helpful in alopecia totalis—except for eyebrows), W, X, Y, Z</td>
<td>Possible teratogenicity of DNCB (another topical sensitizer) led to SADBE substitution</td>
</tr>
</tbody>
</table>

A: Electrodesiccation and curettage; B: Cryotherapy; C: Salicylic Acid; D: Lactic Acid; E: Trichloroacetic/other caustic acids; F: Podophyllin; G: laser; H: 5-Fluoro-uracil; I: Retinoids; J: Interferon; K: Cantharin; L: Formalin; L': Glutaraldehyde; M: Bleomycin; N: Topical corticosteroids; O: Systemic corticosteroids; P: Intralional corticosteroids; Q: Anthralin; R: PUVA (Psoralen and UV-A); S: Inosiplex; T: Bleomycin; U: Surgical excision; V: Vaccination with autogenous-wart extracts; W: Ultraviolet radiation; X: Minoxidil; Y: Dithranol; Z: Zinc sulfate; A': Levamisole; B': Photodynamic inactivation; C': Psychological methods (hypnosis)
VI. Conclusions

Assessment 1: Although squaric acid dibutyl ester is well characterized, it is also known to hydrolyze readily in the presence of water. Since it is so exquisitely sensitive to even small amounts of water, it should only be compounded in media in which there is no water. The impurity profile of SADBE may differ depending on the route of synthesis. SADBE used in compounding could vary significantly from SADBE used in literature studies in the level and types of impurities present; this could result in altered clinical properties and toxicities.

Assessment 2: SADBE is not mutagenic in the Ames assay. Mammalian genotoxicity, chronic toxicity, reproductive toxicity, and carcinogenicity studies have not been conducted with SADBE. Thus, it is not known what the potential toxicities of SADBE are in humans or whether it is likely to be teratogenic in humans.

Assessment 3: There is limited characterization of the human safety profile. Adverse side effects from exposure to SADBE include severe eczematous dermatitis, blistering, lymphoplasia and skin pigmentation changes.

Assessment 4: Many approved products are available for the treatment of verruca and alopecia areata.

Assessment 5: Since its first clinical report in 1980, SADBE has been used as an experimental treatment alternative for alopecia areata and verruca vulgaris. Evidence for current widespread use is not apparent.

Assessment 6: Taking into account the available information, there is minimal evidence that SADBE is effective in the long-term treatment of alopecia areata. Treatment of alopecia areata with SADBE may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped. SADBE is potentially a second or third-line treatment alternative for verruca vulgaris.

VII. Recommendation

Four criteria have been used to evaluate SADBE for inclusion on the bulk drug compounding list: (1) the chemical characterization of the substance; (2) the safety of the substance; (3) the historical use of the substance in pharmacy compounding; and (4) the available evidence of the substance's effectiveness or lack of effectiveness. Our evaluation of SADBE, based on a balanced assessment of each criterion in the context of the others, leads to our recommendation that it is not appropriate for SADBE to be included on the list.
The nonclinical studies conducted to date minimally evaluate the safety of squaric acid dibutylester. The studies do not characterize the potential toxicity to internal tissues nor do they characterize the dermal toxicity from long term topical application. Conclusions about the safety of SADBE cannot be made before such studies are done.

The evidence from historical use suggests that SADBE may be useful as second or third line therapy for warts and possibly as a therapy for alopecia areata. It is our impression that SADBE has become more commonly used as a topical sensitizer than dinitrochlorobenzene (DNCB), largely because the latter compound, available for toxicologic evaluation for more than 20 years, has well-established toxicities. The notion seems to be that the known toxicities of DNCB make it less attractive than the unknown toxicities of SADBE.

If SADBE is not placed on the list of bulk drug substances for compounding, a physician/investigator could still file an investigational new drug application (IND) for use of SADBE in humans. Pursuing this route would provide important and clinically relevant information about: (1) the chemistry of SADBE (i.e., its stability, its comparative solubility in different vehicles), (2) the safety profile – pharmacology/toxicology of SADBE (i.e., safety information about long-term dermal usage), and (3) the clinical side effect profile (i.e., risk of pigmented and eczematous reactions).

References


DMINOPYRIDINES

Table of Contents

FDA Review/Recommendation

Background Information

Tab 1  FDA Selected Literature

Tab 2  Additional background information on 4-aminopyridine provided by the International Academy of Compounding Pharmacists

Tab 3  Selected Public Comments
Aminopyridine Review
FDA Compounding Advisory Committee

General Comments

4-aminopyridine and diaminopyridine are both potassium channel blockers that can be used to enhance the propagation of action potentials along injured axons and to enhance synaptic transmission.

While they could be used interchangeably in these diseases, a review of the literature suggests that most of the experience with chronic spinal cord injury has been with 4-aminopyridine and most of the experience with Lambert-Eaton Myasthenic Syndrome has been with diaminopyridine. Experience in MS seems to be divided between the 2 drugs. These different usage profiles may become important in risk-benefit assessments because Lambert-Eaton Syndrome is an orphan indication with an estimated prevalence of 300 in the US. It is a severely disabling condition for most and life-threatening for a fraction of patients. Diaminopyridine seems to be generally recommended by experts as the first line therapy of choice.

Diaminopyridine is a more potent potassium channel blocker than 4-aminopyridine. It is also less epileptogenic because it crosses the blood brain barrier less readily.

For both drugs, the usual dosing regimen varies from 15-100mg/day in divided doses. This usually produces blood levels on the order of 20-100ng/ml. Peak levels of both drugs can vary widely between subjects and perhaps even within subjects. Both are predominantly excreted by the kidney without biotransformation.

Effectiveness

See the attached literature review by drug and by proposed use.

Safety

4-aminopyridine exists as IR, CR, and SR preparations with progressively lower Cmax's at the same oral dose. No CR or SR formulations of diaminopyridine are mentioned in the literature.
Across all indications, the exposure for both drugs is about 300-400 individuals in the literature.

Common AEs reported include lightheadedness, dizziness, paresthesias, nausea, and abdominal pain. BUT the primary safety concern with both is the occurrence of seizures.

A literature review, ignoring drug overdoses, revealed 3 seizures for diaminopyridine and 6 for 4-aminopyridine. There is a suggestion from the literature that seizures with 4-aminopyridine have occurred at the lower dose range (35 mg/day) while those with diaminopyridine have been at the highest dose range (100mg/day).

**Conclusions**

There is a significant risk of seizures with the use of the aminopyridines. Because the benefit-to-risk ratio can be small and because there is the possibility (yet to be proven) that different formulations may alter the benefit-to-risk ratio, the aminopyridines should not be placed on the pharmacy compounding list at this time. Current experience with these drugs should allow for the accumulation of more data to improve their future safe use.
Chemistry

4-Aminopyridine
[Fampridine]

CAS #: 504-24-5
Molecular Formula: C7H6N2
Molecular Weight: 94.1
Melting Point: 158-159°C

Executive Summary

The physical and chemical properties of 4-aminopyridine have been well characterized in published literature. 4-Aminopyridine is soluble in water, alcohol, slightly soluble in benzene, aliphatic solvents, and is unstable at room temperature if exposed to humidity and light.

Background

4-Aminopyridine was first prepared by A. Kirpal in 1902, R. Camps in 1902, and G.A. Hauser and J. Reynolds in 1950. 4-Aminopyridine is currently commercially available. It is manufactured and supplied by Sigma Chemical Co. It is highly toxic and may be fatal if inhaled, swallowed or absorbed through the skin. A mask and gloves must be worn at all times when handling this material (according to published Material Safety Data Sheets).

Physical and Chemical Properties

4-Aminopyridine is a white to tan crystalline powder. It is soluble in water.

Synthesis

The references describing the synthesis of 4-aminopyridine are very old and not readily accessible. On a production scale, the available information is confidential and not publicly available.

Analytical Chemistry

The production scale material for pharmaceutical use meets the specifications NLT 99 % assay (HPLC), NMT 1% isonicotinamide, synthesis impurity (TLC), NMT 0.5% water content.

Commercial Sources

The following domestic sources have been identified: Sigma Chemical Co. The technical grade material is NLT 98% pure.
Chemistry

3,4-Diaminopyridine
[3,4-DAP]

CAS #: 54-96-6
Molecular Formula: C₅H₅N₃
Molecular Weight: 109.13
Melting Point: 220°C

Executive Summary

The physical and chemical properties of 3,4-DAP have been well characterized in published literature. 3,4-DAP is readily soluble in water, alcohol, insoluble in aliphatic solvents, and is unstable at room temperature if exposed to humidity and light.

Background

3,4-DAP was first prepared as a synthesis intermediate by O. Bremer in 1935, Clark-Lewis, et al. in 1962, and Campbell, et al. in 1986 by different methods. This material is commercially available. It has been has been well characterized. It is stored in tight light-resistant containers to maintain its anhydrous state.

Physical and Chemical Properties

3,4-DAP is a white to creamy white crystalline powder. It is soluble in water. Its structure has been well characterized in the published literature. It has been manufactured on a production scale from the commercial technical grade as well as from 4-aminopyridine as starting material. 3,4-DAP is unstable at room temperature in the presence of moisture or light.

Synthesis

Several methods of synthesis have been published. On a production scale, the following flow chart summarizes the synthesis of 3,4-DAP starting with 4-aminopyridine and affording a yield of 82.2%.
Analytical Chemistry

The production scale material meets the specifications NLT 99.5 % assay (HPLC) and NMT 0.05% 4-aminopyridine synthesis impurity (HPLC).

Commercial Sources

The following domestic sources have been identified: Janssen Chimica, Reilly Industries, Inc, and SAF Bulk Chemicals. The commercial technical grade 3,4-DAP is NLT 98% pure.
4-Aminopyridine and Diaminopyridine

Abbreviations:
- 4-aminopyridine: AP
- diaminopyridine: DAP
- multiple sclerosis: MS
- spinal cord injury: SCI
- Lambert-Eaton myasthenic syndrome: LEMS

Contents:
I. Literature Review: 4-aminopyridine
   Efficacy in Chronic Spinal Cord Injury
   Efficacy in Multiple Sclerosis
II. Literature Review: diaminopyridine
   Efficacy in Multiple Sclerosis
   Efficacy in Lambert-Eaton Myasthenic Syndrome
III. Safety of 4-aminopyridine and diaminopyridine
Attachments
   A. References (full text) from above
   B. Reference Lists for DAP and AP

I. Literature Review: 4-aminopyridine

Efficacy in Chronic Spinal Cord Injury (SCI)


26 pts (2 centers) with chronic (>2yrs) and stable SCI deficits completed this crossover trial (2 week treatment periods with 1 week washout). Dose was 12.5bid for first weeks of active therapy and 17.5bid for 2nd week of active therapy. Primary outcome was a composite endpoint. No difference was demonstrated on this composite endpoint. Nominally significant results favoring AP were seen on a patient global, a patient QOL scale, and a sensory scale. AEs were lightheadedness and nausea which were transient and trivial.

Formulation used: Fampridine-SR (half-life=5.5hrs)
Efficacy in Multiple Sclerosis (MS)


70 pts with MS enrolled in cross-over study. Treatment periods were 12 weeks long with no washout period. The maximum dose was 0.5mg/kg of body weight. The primary outcome was the Kurtzke expanded disability status scale (EDSS): the estimated effect was 0.28 points (P=0.001). A change in Kurtzke score of 1 point or more was seen in 10 (16%) active pts and 0 placebo pts.

No serious AEs seen. No seizures were seen, but one pt had generalized spike-wave discharges recorded on an EEG during 4-AP treatment. However, 2 pts from the study who continued open-label treatment had seizures and one developed hepatitis. (Bever. Neurology. 1994; p 1055)

Common AEs included paresthesias, dizziness, and lightheadedness.

Formulation used: Local hospital in Netherlands

2. Unpublished Study

In 1994, 161 patients with MS enrolled in a randomized, placebo-controlled, parallel-group study. Treatment periods were 6 weeks. The primary outcome variable was the percentage of patients improving on the EDSS. No difference was found between the active and placebo groups; 20% of patients improved in each group.

Formulation used: Fampridine-SR
II. Literature Review: diaminopyridine (DAP)

DAP has greater potassium channel blocking potency in vitro. The proconvulsant activity is lower than 4-aminopyridine, when both are administered systemically to animals. This is because the CSF/serum ratio for 4-AP may be 2 to 3 times greater than for DAP. DAP is not available in a sustained release formulation like 4-AP.

Efficacy in MS


36 pts with MS were enrolled in this crossover trial with 30-day treatment periods separated by a 30-day washout. Primary outcome was improvement in a prospectively defined deficit which was leg weakness for 34/36 pts. The dose was escalated in each treatment arm from 1-20 mg capsule/day up to 5-20 mg capsules/day over 5 days.

22 pts improved on DAP; 2 pts also favored DAP. No effect on EDSS though.

One seizure was recorded during DAP treatment. Dose-limiting AEs were seen in 8 pts. The AEs were paresthesias or abdominal pain in seven and anxiety in one.

Formulation used: University of Maryland under IND

Efficacy in Lambert-Eaton Myasthenic Syndrome (LEMS)


Double-blind, placebo-controlled crossover study with 12 pts. Treatment periods were 3 days long without a washout period. Dosage went as high as 100mg/day. Strength and autonomic symptoms improved. Amplitudes of compound muscle action potentials nearly doubled.
One patient had a seizure after 10 months of treatment on 100mg/day. She continued on DAP at a lower dose. All pts continued on long-term therapy for at least one year.

Formulation used: not stated


Summarizes the Duke University experience over the last 10 years--45 LEMS pts treated with DAP; 40 LEMS pts treated for an average of 31 months. "85% of pts derived functionally significant improvement from DAP." Almost half of all pts achieved normal function.

Dr. Sanders mentions (p813) that he is part of the conduct of an on-going placebo-controlled, double-blind, parallel study to demonstrate that DAP is effective in LEMS.

Of the 45 pts, one had a seizure attributed to DAP. A second pt had a seizure, but had metastatic disease to the brain also. A third pt had a seizure attributed to toxic levels of theophylline.

III. Safety of AP and DAP

PK

The peak plasma levels after oral administration of AP show wide intersubject variation. AP is predominantly renally excreted with no clear evidence of biotransformation. The half-life is about 3.6hrs. Oral preparations exist with immediate and sustained release properties; peak levels vary with the type of preparation.

The half-life and peak levels of DAP varied widely between subjects. Half-life varied from 20min to 2hrs.
Exposure From the Literature

A tabulation of individual patient exposures from the published literature for AP revealed 409 individuals across all diagnostic categories.

A tabulation of individual patient exposures from the published literature for DAP revealed 307 individuals across all diagnostic categories.

Common AEs and Seizures

The common AEs with these drugs are lightheadedness, dizziness, and paresthesias. Nausea and abdominal pain have also been reported.

The primary safety concern with both AP and DAP is seizures.

Seizures were reported in several pts treated with AP for botulinum toxicity. AP concentrations ranged from 35-475ng/mL in those pts (? levels at time of seizures).

AP in MS patients: Two MS pts developed seizures in long term treatment on 0.5mg/kg/day AP. A third MS pt developed an abnormal EEG on the same dose of AP.

A fourth MS pt had a seizure with a plasma level of 104ng/mL AP. A fifth MS pt developed acute confusion with a level of 114ng/mL AP.

AP in SCI patients: No reports of seizures from AP in SCI exist in the literature.

DAP in MS patients: One seizure from DAP in MS is reported in the literature.

DAP in LEMS patients: 4 seizures are reported in the literature with the use of DAP in LEMS. The two without other risk factors were on a dose of 100mg/day. The other two pts had cerebral metastatic disease and theophylline toxicity.

A tabulation of individual patient exposures from the published literature for DAP revealed 307 individuals across all diagnostic categories. Three reported seizures (excluding cases of cerebral mets and theo. toxicity) for
a risk of 1/100.

A tabulation of individual patient exposures from the published literature for AP revealed 409 individuals across all diagnostic categories. Six reported seizures for a risk of 1/68.

**Concomitant Risk Factors for Seizures**

As many as half of all pts with LEMS may have associated malignancy, usually small cell lung cancer. Metastatic lesions in the brain in those pts would, alone, create a seizure risk. MS pts may also have an increased risk of seizures due to cortical or subcortical lesions. Pertinent to this is fampridine reference #127, a case-control study of epilepsy in MS comparing seizure risk to cortical-subcortical lesion load.

No cases of seizures in SCI pts were found in the literature review, but seizures are reported in botulism pts.
January 18, 1999

Robbie Johnson, R.P.H.
Johnson Pharmacy
Fax # (715) 539-2882

Dear Rob:

I received your note regarding 4-AP. I certainly would be happy to acknowledge for you that 4-Aminopyridine used in a number of neuromuscular patients, including MS, myasthenic syndrome, myasthenia gravis, and some peripheral neuropathies, has been quite successful. Patients receive significant palliative relief and improvement in their strength when taking 4-AP. It has been around a long time and the side effect profile has also been quite favorable. Many of my patients with multiple sclerosis and myasthenia gravis heavily rely on this medication to maintain their strength. The other issue that I think is important in these patients who tend to be more sedentary because of their weakness is the fact that with 4-AP they are more able to do therapeutic exercises while on the medication than they would otherwise. I certainly hope the FDA allows us to continue using 4-AP for our patients.

Please let me know if I can be of any further assistance.

Sincerely,

Raymond J. Szmanda, D.O.
Neurologist

RJS/jb
TO: FDA PHARMACY COMPOUNDING ADVISORY COMMITTEE

RE: REQUEST TO INCLUDE 4 AMINOPYRIDINE ON THE BULK DRUGS LIST

I am requesting that the compounded drug 4 Aminopyridine be included on the Bulk Drugs List.

On behalf of my wife, who has multiple sclerosis and myself, we feel that 4AP should continue to be available through the prescription by a physician and compounded by a licensed pharmacist. My wife has taken low doses of 4AP for approximately 6 months with modest but positive results. As clinical research on 4AP has demonstrated in the past, 4AP enhances the neurological conduction through those neurons damaged by the demyelination occurring with MS.

The unique effect of the 4AP in restoring the cellular chemical balance lost from demyelination is important in the potential for improvement in nerve conduction. Most MS patients I have talked to who are taking the drug under prescription are informed as to the potential dangers of overdosing and realize the patient weight-dosage relationship of the drug. As with any drug, there is potential for misuse. This misuse is only prevented by an informed patient with a open discussion between their pharmacist, physician and themselves. My wife who is a veteran of the current therapies for MS including solu-medrol IV, Betaseron, Avonex, Copaxone and a clinical trial participant for Linomide is acutely aware of the potential benefits and side effects of drug therapies for MS. I feel that her experience with trials of drugs is not uncommon in the MS patient community and has created a hardy patient group who are proactive in understanding and meeting the challenge of the disease and symptomology. With MS, many patients I feel are not expecting a cure, but are attempting to improve the quality of their life by taking the available prescribed immuno-modulator drugs with no guarantee of efficacy. I believe by my own observations and discussions with MS patients, discussions with neurologists and by studying the available research information, 4 Aminopyridine does provide a benefit in modest improvement of neurological function. It is understood that 4AP has a short life in the body and dosage is required at timed intervals during the day. It is typical for a patient to spend approximately $50.00 a month for low dosage of 15 mg a day.

My wife and I are involved with the local branch of the National Multiple Sclerosis Society and their support groups. A number of MS patients attending these groups who are taking prescribed 4AP, have expressed disappointment in the event the availability of the drug would be altered.

In closing, I hope I have given the committee information of value in making a decision to include 4 Aminopyridine on the Bulk Drug List and to provide for continue availability to those MS patients and their physicians for which it provides neurological benefit.

Art Hulkoff, B.S., M.P.H
Pharmacy Compounding Advisory Committee

Public Meeting

May 6-7, 1999

Volume 3

Mild Silver Protein
Monosodium Aspartate
Betahistine Dihydrochloride
Cyclandelate
Hydrazine Sulfate

Advisory Committee Conference Room, 1066
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852
Volume 3 contains documentation regarding the following bulk drug substances nominated for inclusion on the list of bulk drugs acceptable for pharmacy compounding that will be discussed at the meeting. Most of the documentation was compiled by the review divisions responsible for these drugs.

- Mild Silver Protein
- Monosodium Aspartate
- Betahistine Dihydrochloride
- Cyclandelate
- Hydrazine Sulfate
MILD SILVER PROTEIN

Table of Contents

FDA Review/Recommendation

Background Information

- The cover sheet provided by the nominator. This includes general information about the substance, including its chemical properties.

- Selected abstracts of articles obtained by FDA from the medical literature attesting to the use of the substance. These are a sampling of articles identified through searches of Medline, Toxline, IRIS, and International Pharmaceutical Abstracts.

- A summary of the toxicological data for the substance prepared by FDA after review of the literature.

- Selected public comments.
Mild Silver Protein

Alternative names: Argyrol, Protargol

Formulations:
OTC: 10% solution in 15 and 30 mL containers
Rx: 20% solution with EDTA in 1 mL dropperettes

Previous manufacturers:
Cooper Laboratories
IOLAB

Marketed Indications:¹ (Note: None of the indications have been “Approved indications”)
1. Treatment of eye infections
2. Preoperatively in eye surgery.
3. Dye before surgical scrub as indicator of the adequacy of preparation.

Drug Interactions:
Sulfacetamide preparations are incompatible with silver preparations

Dosage and Administration:
Preoperatively: Instill 2 or 3 drops into eye(s). Rinse out with sterile irrigating solution.

Infections: Instill 1 to 3 drops into eye(s) every 3 or 4 hours for several days.

Packaging:
Tight, light-resistant containers.

Alternative Medications:
Gentamicin ophthalmic solution, 0.3%
Tobramycin ophthalmic solution, 0.3%
Sulfacetamide sodium ophthalmic solution, 10%
Neomycin, polymyxin B sulfate and gramicidin ophthalmic solution
Trimethoprim sulfate and polymyxin B sulfate ophthalmic solution
Chloramphenicol ophthalmic solution, 0.5%
Ciprofloxacin ophthalmic solution, 0.3%
Norfloxacin ophthalmic solution, 0.3%
Ofloxacin ophthalmic solution, 0.3%

Regulatory History:
Mild Silver Protein (Argyrol) has been marketed since approximately 1910 and as such is not the subject of an approved New Drug Application (NDA). It was the subject of submissions by Cooper Laboratories, Inc. as part of the Ophthalmic Drug Products for Over-the-Counter Human Use Panel Review and subsequent rule-making. Subsequent to the finding that there was insufficient data available to determine that mild silver protein was effective as an ophthalmic anti-infective, marketing was discontinued.

Background:
Therapeutic properties of silver and its salts were recognized as early as the Roman Empire period. Jabir ibn Hayyan Gegber, an Arabian physician of the eighth century, initiated the use of silver nitrate on the eye. The ability of silver ions to kill microorganisms is the basis for their ophthalmic use. Silver nitrate was found to occasionally cause necrosis of conjunctival epithelial cells and a gray-black color when light reduced the salt to its metallic state. In addition, irritation, scarring of the conjunctiva, corneal opacification, and symblepharon occurred. In an attempt to reduce these problems, Albert C. Barnes, MD and Hermann Hille, in 1902, developed a combination of silver nitrate and grain protein (Argyrol). This mild silver protein solution originally was intended to be an antimicrobial agent. The colloidal suspension liberates silver ions that alter the protein in the bacterial cell wall. It also has been suggested that silver interferes with essential metabolic activity of bacteria. The silver in this mild silver protein solution ionizes poorly, and thus causes less irritation than silver nitrate. However, its germicidal effectiveness is also decreased and the adverse experiences were not eliminated.

The 10% and 20% mild silver protein solutions have been available for topical ocular use in the United States as a silver nitrate and gelatin colloid. The drug was available also abroad under a variety of proprietary names and formulations. It is classified in pharmacy textbooks as a local anti-infective agent. The antimicrobial properties of this mild silver protein solution have been questioned for years.

---

2 45 FR 30002-30050. Ophthalmic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Proposed Rulemaking, May 6, 1980.
Safety

In most cases, mild silver protein has been administered safely with minimal adverse experiences. Numerous articles and books have been written concerning silver deposition of the conjunctiva, lacrimal sac, cornea and lens following administration of mild silver protein. The conjunctival deposits under the light microscopic are extracellular silver deposits in the connective tissue cells of the submucosa. The silver deposits in the cornea are located in Descemet's membrane and may occur with clinical conjunctival involvement. In the lacrimal sac, the silver is deposited in the mucosal epithelium. In the lens, it may cause anterior subcapsular discoloration or in the nucleus.

Most reported cases of argyrosis have occurred following at least 2 months of instillation, however, Karcioglu and Caldwell reported a case of ocular argyrosis after only one treatment with Argyrol eye drops. The conjunctival, corneal and lens manifestations are shown below.

Argyrosis is generally permanent and although not usually known to impair visual acuity, has been associated with decreased night vision. Decreased night vision has been correlated with increased levels of silver in both the conjunctiva and the cornea.

---

Staining of lacrimal sac

Staining within the cornea

Silver impregnation of epithelial basement membrane

Involvement of Descemet's membrane

---

Efficacy

In vitro Studies


Bacterial Effect of Nonirritating Concentrations of Antiseptics

<table>
<thead>
<tr>
<th>Antiseptic</th>
<th>Maximum Nonirritating Concentration (%)</th>
<th>Number of Organisms Surviving (%) - <em>Staphylococcus aureus</em> After 1 minute</th>
<th>After 10 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merthiolate</td>
<td>0.1</td>
<td>84.7</td>
<td>70.9</td>
</tr>
<tr>
<td><strong>Argyrol</strong></td>
<td><strong>50 (12.5 used)</strong></td>
<td><strong>55.2</strong></td>
<td><strong>19.8</strong></td>
</tr>
<tr>
<td>Phenyl mercuric nitrate</td>
<td>0.01</td>
<td>53.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Gentian violet</td>
<td>0.01</td>
<td>45.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Chlorazene</td>
<td>0.1</td>
<td>22.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Acriflavine</td>
<td>0.05</td>
<td>19.8</td>
<td>0.46</td>
</tr>
<tr>
<td>Mercurochrome</td>
<td>2</td>
<td>6.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>0.25</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Iodine</td>
<td>0.025</td>
<td>1</td>
<td>0.39</td>
</tr>
<tr>
<td>Alba</td>
<td>0.04</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Comment:** Mild silver protein (Argyrol) was among the least effective of the antiseptics tested.


The in vitro activity of seven metallic compounds was tested against penicillinase (beta lactamase) producing strains of Neisseria gonorrhoeae (PPNG) and non-PPNG strains. On a weight basis, the mercurials showed the greatest in vitro activity.

<table>
<thead>
<tr>
<th></th>
<th>MIC90 Concentration at which 90% of all strains were inhibited (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylmercuric borate</td>
<td>5</td>
</tr>
<tr>
<td>Thiomersal</td>
<td>5</td>
</tr>
<tr>
<td>Mercuric chloride</td>
<td>20</td>
</tr>
<tr>
<td>Silver nitrate</td>
<td>80</td>
</tr>
<tr>
<td><strong>Mild silver protein</strong></td>
<td><strong>200</strong></td>
</tr>
</tbody>
</table>

**Comment:** Mild silver protein (Argyrol) was among the least effective of the antiseptics tested.
Controlled Clinical Studies


32 patients undergoing ophthalmic surgery were studied. No patient had received pre-operative antibiotic therapy or had an infection at the time of surgery. Twenty microliters (1 drop) of 20% mild silver protein solution was instilled in the inferior conjunctival fornix of one randomly selected eye. Hexachlorophene soap was applied equally to both eyelids, eyelid margins, cheeks, nose, eyebrow, and forehead. The inferior fornix of the eye into which the mild silver protein solution had been instilled was then irrigated with a normal saline solution, while the other eye had no irrigation.

<table>
<thead>
<tr>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before preparation</td>
</tr>
<tr>
<td>After preparation</td>
</tr>
<tr>
<td>Colonies</td>
</tr>
<tr>
<td>Untreated</td>
</tr>
<tr>
<td>Mild silver protein</td>
</tr>
<tr>
<td>Species</td>
</tr>
<tr>
<td>Untreated</td>
</tr>
<tr>
<td>Mild silver protein</td>
</tr>
<tr>
<td>Number of Eyes in which Culture was Sterile</td>
</tr>
<tr>
<td>Untreated</td>
</tr>
<tr>
<td>Mild silver protein</td>
</tr>
</tbody>
</table>

"Although the number of colonies and species were greater after the preparation than before in both mild silver protein solution-treated and untreated eyes, in no case was the increase of actual numbers significant at the 5% level by Student's $t$ test. The difference in the amount of increase of actual number in the untreated eye as opposed to the mild silver protein solution-treated eye also was not found to be significant at the 5% level. The pattern of sterile cultures before and after chemical preparation of the eye is given [above]. Of all the eyes in this study, only three of the 15 that were sterile before preparation remained sterile after preparation. The organisms cultured were diphtheroids, Staphylococcus epidermidis, Propionibacterium acnes, Candida albicans, and Klebsiella sp."

Comments: There was no statistically significant difference between groups.


Open-label, non-randomized parallel trial comparing the preoperative application of povidone-iodine to the ocular surface versus mild silver protein (Argyrol) in the reduction of the incidence of endophthalmitis after intraocular surgery. During an 11-month period, topical 5% povidone-iodine was used to prepare the conjunctiva in 1 set of 5 operating rooms, while silver protein solution was used in another set of 5 rooms. In all cases, surgeons continued to use their customary prophylactic antibiotics. A significantly lower incidence of culture-positive endophthalmitis ($p<0.03$) was observed in the operating rooms using povidone-iodine (2 of 3489 or 0.06%) compared with those using silver protein solution (11 of 4594 or 0.24%).

Comment: Povidone-iodine was superior to mild silver protein.
OTC Review Panel 1973-1979

Evaluated: Marketed mild silver protein products containing either 20 or 40 mg of silver per mL of solution.

Panel Conclusions:

Safety: The Panel concluded that there were no toxicity concerns from the use of mild silver protein and that it was safe for OTC use as an anti-infective, provided that the labeling contained a statement warning of the argyria side effect with prolonged use.

Efficacy: Mild silver protein’s effectiveness as an ocular anti-infective has not been documented.

Overall: The claim that mild silver protein is useful in the OTC treatment of minor eye infections requires clinical studies.

12 Ophthalmic Drug Products for Over-the-Counter Human Use
45 FR 30002-30050 May 6, 1980 Proposed Monograph
48 FR 29788-29800 June 28, 1983 Tentative Final Monograph
53 FR 7076-7093 March 4, 1988 Final Monograph
57 FR 60416 December 18, 1992 Final Rule
Literature Summaries:

Goodman & Gilman\textsuperscript{13}

"Mild silver protein (19 to 23\% silver) is still marketed. It is mostly bacteriostatic. It is nonirritating, even mildly demulcent. Claims that mild silver protein penetrates tissue at the site of application because chloride ion does not precipitate the silver are misleading. The large carrier protein molecule penetrates poorly. Fortunately, the colloidal silver preparations are now in a deserved oblivion."

Havener’s Ocular Pharmacology\textsuperscript{14}

"Aseptic preparation of the eye before surgery is important in reducing endophthamitis postoperatively. Silver protein solution has been used during the preoperative preparation of the eye but has been shown to have little to no antimicrobial effect. It is useful in staining mucus and therefore ensuring adequate irrigation at the end of the preparation."

"Preantibiotic treatment of surface infections has included application of a variety of metallic salts, dyes, and so forth. Most of these medications do, indeed, have bacteriostatic or bactericidal activity, but their use on the eye is limited by ocular tolerance. Topical use of most of these medications is now obsolete."

"Not only are the antiseptic solutions used in ophthalmology before the introduction of antibiotics relatively ineffective germicides, but they actually greatly delay healing of corneal epithelial defects and in most instances may cause permanent corneal opacity. Such drugs include 10\% (mild) silver protein, 2\% merbromin (Mercurochrome), 0.5\% zinc sulfate, 1:3,000 benzalkonium chloride (Zephiran), 1:1,000 acriflavin (Neutroflavin), 1:2,500 nitroercol (Metaphen), 1:2,500 thimerosal (Merthiolate), and 1:5,000 mercuric oxy cyanide."

"Tragic results may follow confusion of 10\% silver protein solutions (Argyrol) with 10\% silver nitrate solutions, which may blind a child. A survey of 85 ophthalmologists in 1952 disclosed 17 who had encountered blindness that had resulted from use of excessively strong solutions of silver nitrate. This is largely of historic interest in the 1990s when silver nitrate solution is limited largely to use in some cases of superior limbic keratoconjunctivitis."


A. INGREDIENT NAME:

SILVER PROTEIN MILD NF

B. Chemical Name:

C. Common Name:


D. Chemical grade or description of the strength, quality, and purity of the ingredient:

<table>
<thead>
<tr>
<th>Specifications</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay: (after ignition)</td>
<td>19.0-23.0%</td>
</tr>
</tbody>
</table>

E. Information about how the ingredient is supplied:

Brown, Dark-Brown, or almost black, odorless, lustrous scales or granules, somewhat hygroscopic, and is affected by light.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Belg., Cz., Fr., Hung., It., and Jpn.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:


H. Information about dosage forms used:
   Liquid

I. Information about strength:
   1-20%

J. Information about route of administration:
   Nasal
   Ophthalmic

K. Stability data:

L. Formulations:

M. Miscellaneous Information:
CERTIFICATE OF ANALYSIS

PRODUCT: SILVER PROTEIN MILD
RELEASE #: N

LOT #: 361695G18
GRADE: NF XIII
CODE: D5785

SPECIFICATIONS

RESULT

1. DESCRIPTION
   Black granules
   Conforms

2. Identification
   To pass test
   Passes test

3. Solubility
   To pass test
   Passes test

4. Assay (after ignition)
   19.0 - 23.0%
   19.74%

5. Ionic silver
   No turbidity
   Conforms

6. Distinction from strong silver protein
   To pass test
   Passes test

ATTENTION: TONY HATCHETT

Date: 06/23/97
Prepared by: A. HAZARI
10762
Approved by: 6/97
QUALITY CONTROL REPORT

CHEMICAL NAME: SILVER PROTEIN MILD NF

MANUFACTURE LOT NO.: C64051D10

PHYSICAL TEST

SPECIFICATION TEST STANDARD: USP_/BP_/MERCK_/NF_/MART._/CO.SPECS.

1) DESCRIPTION:
   BROWN, DARK-BROWN, OR ALMOST BLACK, ODORLESS, LUSTROUS SCALES OR
   GRANULES; SOMewhat HYGROSCOPIC, AND IS AFFECTED BY LIGHT.

2) SOLUBILITY:
   FREELY SOLUBLE IN WATER. ALMOST INSOLUBLE IN ALCOHOL, CHLOROFORM
   AND IN ETHER.

3) MELTING POINT:

4) SPECIFIC GRAVITY:

5) IDENTIFICATION:
   A) COMPLIES (B) AS PER NF 10th EDITION 1955.
   B) COMPLIES (C) AS PER NF 10th EDITION 1955.

PASSES: ___________     FAILS: ___________

COMMENTS:

ANALYST SIGNATURE: ___________________    DATE: ___________

PREPACK TEST: ___________    DATE: ___________    INITIAL: ___________

RETEST: ___________    DATE: ___________    INITIAL: ___________
Sanguinaria / Slippery Elm

**Sanguinaria Canadensis**

**Common Names:**
- Sanguinaria
- Slipping Elm
- Sanguinaria

**Description:**
- Deciduous shrub or small tree
- Leaves: Simple, opposite, compound
- Flowers: Small, yellow, in corymbs
- Fruits: Capsules containing many seeds

**Uses:**
- A bark used traditionally in herbal medicine
- Antimicrobial
- Antioxidant
- Anti-inflammatory
- Blood purifier

**Chemical Constituents:**
- Sanguinarine
- Oxylutein
- 2,3-Oxidized***lutein

**Preparations:**
- Tinctures
- Extracts
- Powders

**Precautions:**
- Not to be taken internally
- May cause gastrointestinal distress

**Herbal Application:**
- Use externally for wounds, burns, and minor cuts
- Use internally as astringent for diarrhea

**Contraindications:**
- Not recommended for use during pregnancy

**References:**
- Available on a clinical trial basis.
Epidermal necrolysis. Based on the treatment of 10 cases of necrolysis, it was suggested that treatments for toxic epidermal necrolysis could include avoidance of possible causes of silver nitrate solution 0.25 to 0.5%, with generous washing, with appropriate cooling and electronic monitoring; and daily examination after about four days the compresses could be replaced by cimetidine, thiazides or quinine. The latter two drugs are often followed by hypoglycemia or alchoholism. The solution should be given routinely and stopped if the reaction persists. — C. H. Gosser, Jr., Ann. Surg. 1967, 25, 308.

Glomerulonephritis. Silver nitrate 5% has little effect in vivo or in vivo against glomerulonephritis type 2 — V. R. Coleman et al., Nephron. 1971, 15, 99. Further study — P. Shimizu et al., ibid., 1975, 10, 37.

Hyaluronid Cyst. Intraperitoneal cysts of Echinococcus granulosus were treated with excellent results in 20 patients by freeing the operation area then administering silver nitrate 0.5% to destroy the cysts. — 1. Vazquez and P. Sadik, J. Pediatr. Surg., 1971, 2, 185, per Trop. Dis., Bull., 1971, 51, 185.

Ophthalmia Neonatorum. In a study of the incidence of ophthalmia neonatorum in 120,000 births, it was found that in 91 cases where preparations other than silver nitrate were used the frequency of gonococcal ophthalmia neonatorum was 0.07% whereas silver nitrate was used the rate was 0.1%. Silver nitrate did not always suppress the development of the condition and seemed to be more effective than other agents. While a difference in frequency did not give any evidence, there was little evidence that it did any good. — Cantor, 1949, 1, 111.

Of the 49 states of the USA which had made regulations stating in the course of prophylactic treatment of the eyes of newborn infants, 22 had specified silver nitrate applications. In all cases found to contain over 1% silver nitrate drops when properly packed, handled, and administered. The increasing incidence of gonorrhea has rendered more important prophylactic use of silver nitrate. — P. Barnum, New Engl. J. Med., 1966, 274, 731. Fewer local reactions occurred with pencycline than with silver nitrate preparations. Pencyclines for neonatal prophylaxis should not be standardized, since it did not appear to sensitise infants. — G. W. Nestor and letter, ibid., 275, 1332. Silver nitrate containing less than 2% of silver nitrate were considered to be ineffective. Treatment was effective if applied early and pencycline was advised only in infants whose mothers were known or suspected to be infected. — E. S. Shaw and letter, ibid., 276, 251. See also P. B. Med. J., 1967, 52, 242.

To prevent gonorrhoea ophthalmia neonatorum, a 1% solution of silver nitrate was instilled at birth. The chemical conjunctivitis caused by silver nitrate was of short duration. — P. Theysen, J. Am. med. Ass., 1966, 201, 902.

For reports on the chemical conjunctivitis associated with instillation of silver nitrate eye-drops and recommendations on the solution of the incidence, see Adverse Effects (above).

Pneumorrhagia. Spontaneous pneumorrhagia was successfully treated in 132 patients by preservatives induced silver nitrate; repeated pneumorrhagia was necessary in only 8 patients. It was suggested that this therapy should be used for patients with minor air leaks or those unable to undergo thoracoscopy, or with mediastinal pre-existing lung disease. — J. Anderson and H. Visser, Dis. Chest, 1968, 72, 420, per J. Am. med. Ass., 1968, 201, 581.


Preparations

Metallic Silver Nitrate (B.P. 1961). Argentum Nitricum. Dry, clean, smooth, flat and smoothly moulded for application as a solution is a causative to warm and convulsive. Protect from light.

A similar preparation is included in several pharmaceuticals.


A similar preparation is included in several pharmaceuticals.

Silver Nitrate Solution (B.P. 1955). Contains not less than 15.5% of AgNO3, the remainder consisting of silver nitrate and water. Store in airtight containers. Protect from light.

Silver Nitrate Cream. Silver nitrate, 0.5% or 2.5%. Sulfur- and 2.5% silver nitrate, 0.5% or 2.5% water to 100%. The cream is soluble in water on shaking. The cream is administered for external use when stored for a week in the dark at room temperature; it is shelf-stable. There is no discolouration. — Pharm. Soc. Lab. Progr., 1968.

Eye-drops

Ophthalmic Argentum Nitricum (D.R. or) Silver Nitrate 570 mg, potassium nitrate 1.2 g, and Water for Injections, 500 ml. A similar preparation is included in P.Y. Berk.


Ophthalmic Solutions

Silver Nitrate Ophthalmic Solution (U.S.P. XII, 1967). Argentum Nitricum. Silver nitrate 20 mg and water for injections. A similar preparation is included in several pharmaceuticals. It contains silver nitrate 1% and para-balsam 0.5% as an astringent. Store in airtight containers. Protect from light.

Solutions

Aqueous Silver Nitrate Solution (U.S.F. XII, B.P. 1955). Argentum Nitricum. Silver nitrate 0.05% w/v in water. A solution in water of silver nitrate was prepared from silver nitrate 7 g, water 254 ml, and strong ammonia solution to adjust the pH to 7. The last race precipitated about 53 ml. It contains 0.5% w/v of silver nitrate. Store in a glass-stoppered container or in aqueous solutions.

This solution has been employed in a dental surgery to deposit silver in exposed enamel or to fill small cavities in the tooth. After the solution had been applied to the tooth, it was followed by a reducing agent such as 10% formoldehyde solution or glycerin to cause a deposit of metallic silver. The solution has also been employed in the treatment of fungous infections of the nails.


Proprietary Names

Heidstrafix (Braun, Dent.). Lipas D.A.K. (Dent.). Nova Nitrat Piptette (Lindemann, Ger.).

Silver Products

Silver Protein Eye-drops (B.P. 1961). 0.5%. A solution of silver protein 0.5% with or without sodium nitrate 0.0002%. The solution is an aqueous solution of phenemericuric ocotane or similar to the final sterilised container may be made up. These are found to be stable by alkali. Protect from light.

Proprietary Names

Stullarg (Merck-Schuchardt, Fr.).

Mild Silver Protein Eye-drops (B.P. 1964). Argentum Nitricum. Silver nitrate 0.5%. Silver nitrate 5 mg and water for injections. Store in airtight containers. Protect from light.

Proprietary Names

Stullarg (Merck-Schuchardt, Fr.).

Mild Silver Protein Eye-drops (B.P. 1964). Argentum Nitricum. Silver nitrate 0.5%. Silver nitrate 5 mg and water for injections. Store in airtight containers. Protect from light.
TRATE SOLUTION
Ammoniacal Silver Nitrate, Howe

A solution of silver diammino equivalent of not less than 23.5 and not less than 9.0 Gm. and

704 Gm.
245 ml.
580 ml.
1000 ml.

and dissolve it in the purity temperature and add the last trace of precipitate from isolation is a clear, colorless, almost odorless solution. Its specific gravity is

Solution (1 in 10) responds to the test, page 683.

Solution add a few drops of formaldehyde-precipitate is immediately formed (dissolution of silver nitrate).

Silver Nitrate Solution (1 in 10) add filter, add 5 ml. of sodium hydroxide litmus blue, remains free from even a transient blue.

Dissimilar Solution add 3 ml. the clear filtrate tested in a flame on a solution of sodium or potassium (distinction from

ml. of Ammoniacal Silver Nitrate Solution 10 ml. of nitric acid, and with 0.1 N ammonium thiocyanate is equivalent to 10.79 mg. of Ag.

From a ml. of Ammoniacal Silver Nitrate e sample to a Kjeldahl distillation flask with 50 ml. of water, and add sufficient of the water to make a volume of 200 ml.; add 10 ml. of sodium sulfide T.S. and 50 ml. of a solution of sodium hydroxide (4 in 10). Connect the flask to a condenser, the lower outlet tube of which dips beneath the surface of 50 ml. of 0.5 N sulfuric acid contained in a receiving flask. Distill the mixture until about 100 ml. of distillate has been collected, add methyl red T.S., and titrate the excess acid with 0.5 N sodium hydroxide. Each ml. of 0.5 N sulfuric acid is equivalent to 3.135 mg. of Ag.

The ratio between the weight of Ammoniacal Silver Nitrate and the percentage of silver nitrate in the precipitate is about 0.79. Package and store—Store Ammoniacal Silver Nitrate Solution in small glass-stoppered, light-resistant containers, or in light-resistant ampoules.

Topical Use—Mix Ammoniacal Silver Nitrate Solution with a reducing agent, such as formaldehyde (1 in 10) or eugenol, to deposit the metallic silver, in a state of fine subdivision, in the desired area of the tooth.

Category—Protective (dental).

SILVER PROTEIN

Argentum Proteinicum Mite Mild Protargol

Mild Silver Protein is silver rendered colloidal by the presence of, or combination with, protein. It contains not less than 19 per cent and not more than 23 per cent of Ag.

Caution: Solutions of Mild Silver Protein should be freshly prepared or contain a suitable stabilizer, and should be dispensed in amber-colored bottles.

Description—Mild Silver Protein occurs as dark brown or almost black, shining scales or granules. It is odorless, is frequently hygroscopic, and is affected by light.

Solubility—Mild Silver Protein is freely soluble in water, but almost insoluble in alcohol, in chloroform, and in ether.

Identification—

A: Heat about 100 mg. of Mild Silver Protein in a porcelain crucible until all carbonaceous matter is burned off. Warm the residue with 1 ml. of nitric acid, dilute with 10 ml. of water, and add a few drops of hydrochloric acid: a white precipitate is produced which dissolves in ammonia T.S.

B: Ferric chloride T.S. added to a solution of Mild Silver Protein (1 in 100) discharges the dark color and a precipitate is gradually produced.

C: To 10 ml. of a solution of Mild Silver Protein (1 in 100) add a few drops of mercury bichloride T.S.; a white precipitate is formed and the supernatant liquid becomes colorless or nearly so.

Ionic silver—To 10 ml. of a solution of Mild Silver Protein (1 in 100) add 2 ml. of a solution of sodium chloride (1 in 100): no turbidity is produced.

Distinction from strong silver protein—Dissolve 1 Gm. of Mild Silver Protein in 10 ml. of water. Add, all at once, 7 Gm. of ammonium sulfate, and stir occasionally for 30 minutes. Filter through quantitative filter paper into a 50-ml. Nessler tube, returning the first portions of the filtrate to the filter, if necessary, to secure a clear filtrate, and allow the filter and precipitate to drain. Add to the clear filtrate 25 ml. of a solution of acacia (1 in 100). In a second 50-ml. Nessler tube dissolve 7 Gm. of ammonium sulfate in 10 ml. of water, and add to this solution 25 ml. of the solution of acacia and 1.4 ml. of 0.01 N silver nitrate. To each tube
Database: Medline <1966 to present>

<1>
Unique Identifier
83203583
Authors
Isenberg S. Apt L. Yoshimuri R.
Title
Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution.
Source
Abstract
Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.

<2>
Unique Identifier
83142687
Authors
Apt L. Isenberg S.
Title
Chemical preparation of skin and eye in ophthalmic surgery: an international survey.
Source
Abstract
We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver
protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.
March 8, 1999

Subject: Mild Silver Protein (MSP)

While MSP is well characterized chemically and has a long history of medicinal use, there is also a whole body of evidence indicating that it was neither safe nor effective in any of its historical uses, including as a treatment for conjunctivitis or as a means of sterilizing the eye before surgery.

The best known brand of MSP, Argyrol, was marketed in the US at least until 1996. It had been developed and introduced to commerce by Dr. Alfred C. Barnes around 1902. Many silver drugs were fraudulently advertised for decades. Argyrol in particular has been singled out as one of the most fraudulently advertised. The ingestion of silver causes argyria, gray skin. Look at my photos. I have argyria which I developed about 40 years ago from taking nose drops that contained silver that a doctor in N.Y. prescribed for me. I am not certain, but I believe that the pharmacist compounded the drops since the only label that they ever had was one that he typed out and pasted on. It never showed a brand name. We always referred to them as “the drops”.

Every form of silver used therapeutically has caused argyria. Many cases were caused by Argyrol although that never stopped the company from advertising it as “nontoxic”.

It is well known that MSP put in the eye caused many cases of argyrosis, the deposition of silver salts in the conjunctiva, lacrimal sac and cornea. Referring to argyrosis, Hill and Pillsbury state that, “...in severe cases the degree of cosmetic disfigurement may be marked. The color varies from light bluish-gray to a brownish-black.”

There is one case report in the literature that is unusual because just one use of Argyrol drops (1% solution MSP) resulted in argyrosis.

In 1983 an article reported a study in which the effectiveness of MSP as a chemical preparation of the eye before surgery was studied. Thirty-two patients had one eye treated with it. Bacteriologic analysis found that MSP was ineffective in reducing the number of species and colonies of bacteria found in the eye. It was reported that many surgeons used it merely because it acted as a stain enabling them to see debris and mucus that had not been already washed out. When this happened, the eye was
irrigated again. The authors pointed out that that had to be weighted against the finding that irrigation itself caused an increase in the bacterial flora of the conjunctiva."

SUMMARY:
Based on the evidence that MSP has been shown to be unsafe and ineffective as an ophthalmologic drug and on the potential of its being abused and used to treat systemic illnesses for which it is equally ineffective and far more dangerous, I request that it not be added to the list of bulk drugs.

Rosemary Jacobs,
Private Citizen
Victim of Greed Passed Off As Science
http://homepages.together.net/~rjstan/
3 http://homepages.together.net/~rjslan/
4 Puckner, WA. Council on Pharmacy and Chemistry JAMA March 17, 1928 p.849-51
5 Gaul, LE, Staud, AH. Clinical spectroscopy JAMA April 20, 1935 p.1387-90
7 Hill, WR, Pillsbury, DM. ARGYRIA THE PHARMACOLOGY OF SILVER The Williams & Wilkins Company 1939 p. 130
8 Hill & Pillsbury p.28
9 THE EYE, EAR, NOSE & THROAT MONTHLY Vol. XXXI #1 Jan. 1952 p. 24
10 Hill & Pillsbury p. 112-5
11 Hill & Pillsbury p. 116
12 Karcoglu, ZA, Caldwell, DR. Corneal argyrosis: histologic, ultrastructural and microanalytic study CAN J OPHTHALMOL vol. 29 #7 1965p. 257-60
13 Puckner, WA. Council on Pharmacy and Chemistry JAMA March 17, 1928 p.849-51
Nomination of monosodium aspartate for inclusion in the list of "approved bulk substances for compounding purposes" was received from Central Admixture Pharmacy Services, Inc. (Docket No. 98N-0182), one commercial source of the substance. The proposed use is as a cardioplegic solution.

**Background**

**Aspartate**

Aspartic acid (HO₂CCH₂CH(NH₂)CO₂H, FW 133.10) is a non-essential amino acid that is readily synthesized from (and converted to) carbohydrate by way of alpha-ketoglutaric acid and therefore can be involved in priming the respiratory chain. Since aspartic acid is an acid it can be supplied as a salt (either sodium or potassium) and aspartic acid is then called aspartate. It can exist in the D, L, or DL. The L form of amino acids are those found in the body.

**The electrical activity of the heart**

Increasing the concentration of K⁺ outside the cell (that is in the perfusion medium, be it blood or anything else) depolarizes the cell and makes it impossible for the cell to be electrically effective. The concentration outside the cell must remain high (i.e., above 8 to 10 mEq/L or so). As soon as it begins to approach normal the heart will resume its electrical activity. This is an entirely reversible phenomenon and simply a function of the ratio K⁺ concentration inside and the K⁺ concentration outside the cardiac (or any other electrically excitable) cell membrane. The utility of infusing KCl solutions for purposes of stopping the heart has been known for centuries, although it has never been evaluated in any form of randomized clinical trial.

**Rationale**

The need to have the operative field relatively blood free, for purposes of visibility, combined with the demonstration that blood cardioplegia is "better than crystalloid cardioplegia (which gives the best visibility) has led to dilution of whole blood by adding components that dilute the blood and "preserve" myocardial function. Dilution of blood for cardioplegic solutions vary from 4:1 to 8:1. An example of a 4:1 dilution follows.

<table>
<thead>
<tr>
<th>Purpose (Perfusion for the duration of aortic cross-clamp)</th>
<th>Added Substance</th>
<th>For Component</th>
<th>Final Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Induction (Stops the Heart)</td>
<td>KCl</td>
<td>K⁺</td>
<td>18-20 mEq/L</td>
</tr>
<tr>
<td></td>
<td>KCI</td>
<td>pH</td>
<td>7.2 to 7.8</td>
</tr>
<tr>
<td></td>
<td>THAM</td>
<td>Ca⁺⁺</td>
<td>0.5 to 0.6 mM/L</td>
</tr>
<tr>
<td></td>
<td>CPD*</td>
<td>Osmolarity</td>
<td>340 to 360 mOsm</td>
</tr>
<tr>
<td></td>
<td>D5 &amp; 1/4 NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm Induction (Stops the Heart)</td>
<td>KCl</td>
<td>K⁺</td>
<td>20 to 25 mEq/L</td>
</tr>
<tr>
<td></td>
<td>KCI</td>
<td>pH</td>
<td>7.5 to 7.6</td>
</tr>
<tr>
<td></td>
<td>THAM</td>
<td>Ca⁺⁺</td>
<td>0.15 to 0.25 mM/L</td>
</tr>
<tr>
<td></td>
<td>CPD*</td>
<td>Glucose</td>
<td>&gt; 400 mg%</td>
</tr>
<tr>
<td></td>
<td>Glutamate/Aspartate</td>
<td></td>
<td>13 mM/L each</td>
</tr>
<tr>
<td></td>
<td>5% D&amp;W Osmolarity</td>
<td></td>
<td>380 to 400 mOsm</td>
</tr>
<tr>
<td>Cold Maintenance (Perfusion for the duration of aortic cross-clamp)</td>
<td>KCI</td>
<td>K⁺</td>
<td>8 to 10 mEq/L</td>
</tr>
<tr>
<td></td>
<td>KCI</td>
<td>pH</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>THAM</td>
<td>Ca⁺⁺</td>
<td>0.5 to 0.6 mM</td>
</tr>
<tr>
<td></td>
<td>CPD*</td>
<td>Osmolarity</td>
<td>340 to 360 mOsm</td>
</tr>
<tr>
<td>Warm Reperfusionate (Just before starting the heart)</td>
<td>KCl</td>
<td>K⁺</td>
<td>8-10 mEq/L</td>
</tr>
<tr>
<td></td>
<td>KCI</td>
<td>pH</td>
<td>7.5 to 7.6</td>
</tr>
<tr>
<td></td>
<td>THAM</td>
<td>Ca⁺⁺</td>
<td>0.15 to 0.25 mM/L</td>
</tr>
</tbody>
</table>

1 Cardioplegia is defined as an elective procedure for stopping cardiac activity temporarily.
Comments from the literature
Buckberg, et. al. wrote in the Journal of Cardiac Surgery (Volume 10, pages 68-89):
"In the past, we formulated four cardioplegic solutions comprised of a high- and low-K⁺ amino acid-enriched solution for warm induction and reperfusion, and a high- and low-K⁺ nonamino acid-enriched solution for cold induction and maintenance doses. These solutions differed only in the K⁺ content of the amino acid and nonamino acid formulations. Currently, only two cardioplegic solutions are made up for each procedure. The high-K⁺ (20 mEq/L) solution contains glutamate/aspartate, low Ca⁺⁺ (0.2 to 0.3 mM), and the other components we have used previously. This solution (1) arrests the heart promptly during either warm or cold induction, (2) remains available if electromechanical activity recurs during the procedure, (3) provides for substrate enrichment if warm induction is used (high-risk patients, unexpected hemodynamic compromise, impaired cardiac function), and (4) comprises the warm reperfusate; our recent studies confirm the safety of using 20 mEq KCl solution for warm reperfusion, rather than the 10 mEq/L solution used previously. The low-K⁺ (10 mEq/L) solution is used for maintenance doses during intermittent cold cardioplegic infusion. Glutamate and aspartate are not added to the maintenance solution, as peripheral vasodilatation may occur when large volumes of amino acids are used. Infusion of this maintenance solution may be started as soon as the heart arrests during cold cardioplegic induction, if there is a desire to limit the glutamate/aspartate, hypocalcemic infusion to the terminal warm reperfusate."

Rozenkranz, et. al. (J. Thoracic and Cardiovascular Surgery, 91:428-435, 1986) have shown that in patients, the addition of glutamate and aspartate to blood cardioplegic solutions produced better postoperative ventricular function than did blood alone.

Comments on safety
The usual amino acid nitrogen concentration in plasma is in the range of 3 to 6 mg%. The 26 mM of combined aspartate/glutamate would add significantly to the amino acid nitrogen of plasma, amounting to an addition of around 20 mg% (N being about 10% of aspartate's and glutamate's FW). Given that amino acids form the substrate for a variety of metabolic cycles, this represents a small additional amount of amino acid load.

It should be noted that the aspartate/glutamate blood solutions are used only for induction and reperfusion, not for the duration of cardioplegia. Experience has been that use of aspartate/glutamate solutions throughout cardioplegia lead to systemic hypotension.

Summary
There is adequate laboratory and clinical experience with the addition of aspartate to cardioplegic solutions (be it blood or crystalloid, and be it for cardioplegia or other purposes of supporting isolated organs) to warrant the inclusion of both substances in the "Bulk Drug Substances To Be Used in Pharmacy Compounding." From the data available, there is no suggestion of a safety concern provided it is used only for the periods of induction and reperfusion.

The nature of the salt (sodium or potassium) is relevant, therefore the listing should be limited to the monosodium salt. Monopotassium salts although suitable as a supply of amino acid, would supply too much potassium (23 mEq/L) if both aspartate were added as the Monopotassium salt.
References


Additional References


November 19, 1998

Dockets Management Branch
HFA-305
Food and Drug Administration
U.S. Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Bulk Drug Substances To Be Used in Pharmacy Compounding:
Request for Nominations
Docket No. 98N-0182

Dear Sirs:

I am responding on behalf of Central Admixture Pharmacy Services, Inc., to the Food and Drug Administration’s (FDA) Notice and Request for Nominations entitled, “Bulk Drug Substances To Be Used in Pharmacy Compounding.” This notice was published in the April 7 issue of the Federal Register [63 Fed.Reg.17011]. The FDA is seeking candidates for a list of bulk drug substances that can be used in pharmacy compounding that do not have a United States Pharmacopeia (USP) or National Formulary (NF) monograph and are not components of approved drugs.

Central Admixture Pharmacy Services, Inc., would like to nominate the following drug substance:

1. Monosodium Aspartate. This drug is compounded and used in cardioplegic solutions for open heart surgery. See attached articles for indications and efficacy.

I hope this information is helpful, and I ask that you give this nomination favorable consideration. I thank you in advance for your time and attention to this matter. If you have any questions, please do not hesitate to contact me at Central Admixture Pharmacy Services, Inc., 211 Summit Parkway, Suite 122, Homewood, AL 35209, or Ph: (205) 945-1955, extension 17.

Sincerely,

Wm. John Brandon
Vice President Operations
Central Admixture Pharmacy Services, Inc.

Enclosure
BETAHISTINE DIHYDROCHLORIDE

Table of Contents

FDA Review/Recommendation

Background Information

Tab 1 The following is included:

- The cover sheet provided by the nominator. This includes general information about the substance, including its chemical properties.

- Selected abstracts and references obtained by FDA from the medical literature attesting to the use of the substance. These are a sampling of articles identified through searches of Medline, Toxline, IRIS, and International Pharmaceutical Abstracts.

- A summary of the toxicological data for the substance prepared by FDA after review of the literature.

- A bibliography prepared by FDA of articles identified through a search of the medical literature concerning the substance. This bibliography is not exhaustive.

Tab 2 Additional background information on betahistine hydrochloride provided by the International Academy of Compounding Pharmacists
Betahistine Review
FDA Compounding Advisory Committee

General Comments

At one time, betahistine was approved for marketing in the US, labeled for use in Meniere's Syndrome. Betahistine, under the trade name Serc, was the subject of NDA 14-241 approved in the 1960's for marketing in the United States. The commercial sponsor was Unimed, Inc. In 1970, the Commissioner of FDA withdrew approval of the NDA after the discovery that the submission contained unsubstantiated information about some patients in the efficacy studies upon which approval was based. Betahistine has continued to be marketed in other countries however.

Now, betahistine is being considered for pharmacy compounding because of its use in vertigo associated with Meniere's Disease.

Betahistine is a histamine agonist. It is a vasodilator and it also appears to act directly on neurons in the vestibular nuclear complex. It has wide use throughout the world in the treatment of vertigo, especially the vertigo associated with Meniere's Disease. Meniere's Disease causes a triad of symptoms: tinnitus, vertigo, and stepwise hearing loss. While of unknown etiology, its pathophysiology is believed to be related to swelling of the endolymphatic sac in the inner ear. While there are no interventions to prevent the hearing loss, numerous medications are proposed to treat the tinnitus and vertigo. Surgical procedures have also been proposed, to include endolymphatic drainage and section of the vestibular nerve.

Effectiveness in Vertigo of Meniere's Disease

The reference list for betahistine is extensive and is included with this review. Following are several quotes from those references.

"Histamine analogues directly reduce inner ear fluid pressure mainly by increasing the cochlear blood flow, and are probably the treatment of choice [for Meniere's]."\textsuperscript{18}

"It appears that only betahistine and diuretics have a proven effect in double-blind studies on long-term control of vertigo in Meniere's
disease."\textsuperscript{10}

"From clinical studies, it appears that betahistine is an effective agent for the symptomatic treatment of Meniere's syndrome. Efficacy has also been shown in the treatment of patients suffering from paroxysmal vertigo."\textsuperscript{36}

The bibliography provided outlines several small, single center clinical trials with enrollments of 10-50 patients. Some are parallel design; some are crossover studies, with or without washout periods. Some are placebo-controlled; some are active-controlled (usually using calcium channel blockers). Some of the active-control trials demonstrate superiority of betahistine. Some of the active-control trials demonstrate inferiority. And some demonstrate equivalence of the active agents used.

In addition to the clinical evidence, there is also some preclinical evidence that betahistine improves recovery time after vestibular nerve lesions in cats.

\textbf{Safety}

Meanwhile, the safety profile from the literature appears to be benign. There is a single case report of acute bronchospasm. There have been some extrapyramidal reactions. And some rashes are reported. Otherwise the most common AE appears to be GI upset.

\textbf{Conclusions}

There is some evidence for the effectiveness of betahistine in vertigo associated with Meniere's Disease and the drug appears to be well-tolerated.
Chemistry

Betahistine hydrochloride
[N-methyl-2-pyridineethanamine dihydrochloride]

\[
\text{CHEMISTRY} \\
\text{Betahistine hydrochloride} \text{ CAS #: } 5579-84-0 \\
\text{Molecular Formula: } C_{14}H_{13}N_2 \text{ 2HCl} \\
\text{Molecular Weight: } 209.1 \\
\text{Melting Point: } 148-149^\circ C
\]

Executive Summary

The physical and chemical properties of betahistine hydrochloride have been characterized in published literature. No solubility data were found for the hydrochloride salt. Betahistine is a liquid soluble in water. No published analytical data were readily available.

Background

Betahistine was first prepared by Loffler in 1904, then Walter et al. in 1941. Betahistine hydrochloride is currently commercially available. It is manufactured and supplied by Sigma Chemical Co. No information was readily found on the storage and handling of this material.

Physical and Chemical Properties

Betahistine hydrochloride is crystallized from alcohol, m.p. 148-149°C.

Synthesis

The references describing the synthesis of betahistine are very old and not readily accessible. On a production scale for the hydrochloride, the available information is confidential and not publicly available.

Analytical Chemistry

No published information readily available.

Commercial Sources

The following domestic sources have been identified: Sigma Chemical Co. No information was found on the purity of the commercial material.
A. INGREDIENT NAME:

BETAHISTINE DIHYDROCHLORIDE

B. Chemical Name:

N-Methyl-2-(2-pyridyl)ethylamine dihydrochloride

C. Common Name:

Ger., Egypt, Greece, Neth, Switz, U. K. Ser. *See file for various names in different countries.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Quality Assay Tot. base (%): 98.965

E. Information about how the ingredient is supplied:

White to off white crystals, is odorless, crystals obtain from alcohol

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:


**H. Information about dosage forms used:**

Scored tablets

**I. Information about strength:**

4mg in Canada
8mg in U. K.

**J. Information about route of administration:**

Orally

**K. Stability data:**

Melting point: 152° C to 154 C
Incompatibilities:
- Acids
- Acid Chlorides
- Acid Anhydrides
- Oxidizing Agents

**L. Formulations:**

**M. Miscellaneous Information:**
CYCLANDELATE

Table of Contents

FDA Review/Recommendation

Background Information


Tab 5  The following is included:

- The cover sheet provided by the nominator. This includes general information about the substance, including its chemical properties.
- Selected abstracts and references obtained by FDA from the medical literature attesting to the use of the substance. These are a sampling of articles identified through searches of Medline, Toxline, IRIS, and International Pharmaceutical Abstracts.
- A summary of the toxicological data for the substance prepared by FDA after review of the literature.
- A bibliography prepared by FDA of articles identified through a search of the medical literature concerning the substance. This bibliography is not exhaustive.

Tab 6  Additional background information provided by the International Academy of Compounding Pharmacists
Cyclandelate Review  
Pharmacy Compounding Advisory Committee  

CYCLANDELATE AND MIGRAINE  

General Comments  

At one time, cyclandelate was approved for marketing in the US, labeled for use in two indications: 1) as a treatment for intermittent claudication, and 2) as a treatment for cognitive dysfunction in patients suffering from dementia. Cyclandelate had been approved at a time when the Food, Drug, and Cosmetic Act required only proof of safety. In 1962, the act was amended to provide that drugs could no longer be approved unless both safety and efficacy had been proved. After subsequent reviews and appeals, the Commissioner issued a final order in 1996 which withdrew approval of the NDA because of a lack of substantial evidence of effectiveness for those labeling claims.  

Now, cyclandelate is being considered for pharmacy compounding because of its use in both in the treatment of migraine and in the treatment of diabetic retinopathy. First, the use of cyclandelate in migraine will be reviewed and then the use of cyclandelate in diabetic retinopathy will be reviewed.  

Cyclandelate is a calcium entry blocker with vasodilator activity. Migraine is a clinical disorder with a predisposition to intense, usually throbbing headaches. The vascular theory of migraine argues that headaches begin with a period of vasoconstriction, followed by vasodilation. Individual headaches can be treated acutely with analgesics or vasoactive agents. Alternatively, some patients benefit by taking prophylactic medications on a regular basis with the hope of decreasing the frequency and severity of headaches. Several agents are approved for migraine prophylaxis in the US, to include Inderal and Depakote. While no calcium channel blocker is approved for migraine prophylaxis in the US, calcium channel blockers are used off-label for migraine prophylaxis.  

Effectiveness in Migraine  

Several small studies have been published in the past 10 years addressing the use of cyclandelate in migraine prophylaxis.  

In one study\(^1\), patients were randomized to cyclandelate (n=81), propranolol (n=78), or placebo (n=55) and treated for 12 weeks. Both cyclandelate (1200mg/day) and propranolol (120mg/day) performed better than placebo on several measures, but not significantly so. Cyclandelate was well tolerated.  

Another report\textsuperscript{2} suggests that higher doses of cyclandelate (1600mg/day) may be more effective.

Other published studies report similar findings.

\textit{Safety}

Cyclandelate appeared to be well-tolerated based on the 5 published references in migraine populations.

Additionally, in a group of 97 abstracts referencing cyclandelate from 1960-present, no serious adverse events related to cyclandelate are obvious.

The spontaneous adverse event reporting system at the FDA was also searched and contains 34 reports for cyclandelate, covering the years 1971-1996.

Five of the 34 patients had serious AEs, including 1 death, a sudden death in a 71 year-old woman who had been on cyclandelate for 3 months.

Other AEs are, for the most part, single reports of AEs in an elderly population using cyclandelate for peripheral vascular disease. As such, it is impossible to ascertain causality for any of the events.

\textit{Conclusions for Migraine}

There is some evidence for the effectiveness of cyclandelate in migraine and the drug appears to be well-tolerated.

\textbf{CYCLANDELATE AND DIABETIC RETINOPATHY}

Cyclandelate is being considered for pharmacy compounding because of its use in the treatment of diabetic retinopathy.

Diabetic retinopathy\textsuperscript{3} is the most common cause of blindness. It is a characterized by a nonproliferative phase of microaneurysms, retinal hemorrhages, retinal edema, and exudates followed by a proliferative phase of new capillaries and vitreoretinal traction. Good glycemic control appears to be of benefit in the prevention of diabetic retinopathy.\textsuperscript{4}

\textsuperscript{3} Cecil Textbook of Medicine, 19th edition, (1992), pages 1307-1308.
Methods

A Medline search was conducted looking for 'cyclandelate' and 'diabetes' or 'diabetic retinopathy' in the years between 1966 and present. Two relevant publications were identified and are reviewed in the paragraphs below. A search for references to these publications uncovered no additional relevant studies.

Effectiveness in diabetic retinopathy

Cunha-Vaz and colleagues\(^5\) randomized 24 subjects, age 26 to 80, with diabetes but no ophthalmological pathology by history, visual acuity, ophthalmological exam with slit-lamp, or retinal fluorescein angiography, to placebo or cyclandelate 400 mg qid for 3 months. The study monitored, at monthly intervals, extravasation of intravenous fluoroscein dye into the vitreous. One pair of subjects did not complete. Mean results from the remaining 22 subjects are shown in Figure 1 (mean ± s.e.m; adapted from the published Table 1).

![Figure 1. Change in fluorescein penetration (Cunha-Vaz et al.).](image)

The authors claim statistical and clinical significance for this difference in disease progression. The reviewer's opinion is that the first appearance of this effect in the third month is implausible.

A similar study was conducted among 26 subjects at the same institution\(^6\) in Portugal, but subjects were treated and followed for 12 months. Fluorescein angiography demonstrated no differences between placebo- and cyclandelate-treated subjects with regard to microaneurysms. Fluorescein penetration data are shown in Figure 2 (mean ± s.e.m; adapted from the published Table 5).


Although a nominally statistically significant treatment effect is claimed for the right eye, the differences between the groups are most likely the result of differences at baseline and are not attributable to treatment with cyclandelate.

No safety data were presented with either study.

Comments and recommendation for diabetic retinopathy

Increased permeability of retinal vessels, as assessed by extravasation of fluorescein, is an early feature of the nonproliferative phase of diabetic retinopathy. A link between increased vascular permeability and other features of diabetic retinopathy is plausible. Good glycemic control decreases permeability and reduces progression of retinopathy.

These two small studies provide some evidence of an effect of cyclandelate on the permeability of retinal vessels, but the evidence must be characterized as weak. Evidence linking this effect, if any, to progression of other features of diabetic retinopathy is completely lacking. Cyclandelate should not be approved for pharmacy compounding on the basis of its usefulness in the treatment of diabetic retinopathy.
Additional References


CYCLANDELATE

Chemistry

α-hydroxybenzeneacetic acid, 3,3,5-trimethylcyclohexyl ester

mandelic acid, 3,3,5-trimethylcyclohexyl ester

CAS# 456-59-7

Mol Wt. 276.36

Mol. Formula C_{17}H_{24}O_{3}

Melting Point 55.0-56.5°C

Executive Summary

The physical and spectroscopic properties of cyclandelate have been well characterized in published literature (see Anal. Profiles of Drug Substances and Excipients, Vol 21, pg 150-168). Cyclandelate is a mixture of 4 stereoisomers (2 enantiomeric pairs). It is insoluble in water, very soluble in methanol and chloroform and freely soluble in toluene, acetomitrile, ethyl acetate and dimethylformamide (USP classification). Cyclandelate can decompose by hydrolysis to mandelic acid and 3,3,5-trimethylcyclohexanol. However, when cyclandelate is formulated into capsules, this degradation has been shown to be slow—less than 5% in 66 months at ambient temperature. Cyclandelate can also be oxidatively degraded to 3,3,5-trimethylcyclohexyl phenylglyoxalate. There are a number of ways of quantitatively assaying cyclandelate—titrmetry, gas chromatography and HPLC.

Background

Cyclandelate is simply an ester of mandelic acid and 3,3,5-trimethylcyclohexanol and has 3 stereogenic centers. It was originally synthesized by reacting dl-mandelic acid with 3,3,5-trimethylcyclohexanol (as a mixture of cis and trans isomers). More recent procedures for synthesizing cyclandelate utilize only the low melting (cis) isomer of 3,3,5-trimethylcyclohexanol because it is known that esters of mandelic acid with the higher melting trans isomer of 3,3,5-trimethylcyclohexanol are twice as toxic. The synthesis using only the cis isomer gives a mixture of 4 isomers with the following absolute configurations at the 3 centers of asymmetry:

SRR, RSS, RRR, SSS. There are 2 pairs of enantiomers in this mixture.

Physical and Chemical Properties

Cyclandelate is a white to off-white amorphous powder with a slight menthol like odor. It is an ester and consequently susceptible to hydrolytic cleavage in both acid and base.

Analytical Chemistry

Cyclandelate has been characterized by standard analytical techniques and the data are available in the published literature. Both the $^1$H and $^{13}$C spectra show the presence of 2 diastereomers. The electron impact mass spectrum shows a weak M$^+$ peak at m/e 276 and strong fragmentation peaks at m/e 125 and 107 corresponding to loss of the trimethylcyclohexyl and benzhydryl moieties. There are a number of
reports in the literature dealing with the separation of cyclandelate from its impurities and degradation products as well as other pharmaceuticals using gas chromatography.

Commercial Sources

Chem Sources International lists a number of suppliers of cyclandelate – Aceto Corp, Alfa Chem, Ohno Chem Co of Japan and Sigma to name a few. Although listed in the Sigma 1997 catalog, it seems to be no longer available from this source since it is missing from the 1998 catalog. It is not known whether the substance is still being sold as a mixture of isomers.

Reviewed by:

K. Srinivasachar  
Chemistry Team Leader  
Div. of Cardio-Renal Drug Products
A. INGREDIENT NAME:

CYCLANDELATE

B. Chemical Name:

Alpha-Hydroxy-, 3,3,5-Trimethylcyclohexyl Ester (9CI), BS 572, Capilan, Ciclospasmol, Alpha-Hydroxybenzeneacetic Acid 3,3,5-Trimethylcyclohexyl Ester, Sancyclan, Sepyron, 3,3,5-Trimethylcyclohexanol, Alpha-Phenyl-Alpha-Hydroxyaxetate, 3,5,5-Trimethylcyclohexyl Amygdalate, 3,3,5-Trimethylcyclohexyl Mandelate, Methylcyclohexyl Mandelate.

C. Common Name:

Arto-espasmol, Perebral, Saiclate
Cyclobral, Spasmione, Spasmocyclion, Spasmocyclone
Cyclospasmol
Benzenenacetic Acid, Clandilon, Cyclandelate, Cycloyt, Cyclomandol, Cyclospasmol

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay 99.8%

E. Information about how the ingredient is supplied:

A white to off-white amorphous powder with a slight menthol-like odor and a bitter taste.

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:


Harding, F. A. Angiology, 1978;29:139.


Diener, H. C., Foh, M., and Iaccarino, C. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study Group. In summary, cyclandelate has a comparable efficacy to that of propranolol. Both drugs were better than placebo. Both active treatments were well tolerated. Cephalalgia, 1996; 16(6):441-447.


**H. Information about dosage forms used:**

Capsules
Tablets
Suspension

**I. Information about strength:**

1.6g daily
400 mg Tablets and Capsules
400 mg/5ml Suspension

**J. Information about route of administration:**

Oral or Intravenous

**K. Stability data:**

Melts at about 50-53°
Cyclandelate can decompose by hydrolysis to mandelic acid.
Cyclandelate capsules concluded that less that 5% of the cyclandelate degraded in 66 months at ambient temperatures.

**L. Formulations:**

**M. Miscellaneous Information:**
FDA now gives notice that the committee is soliciting comments and information on additional proposed new monographs and proposed changes to certain current monographs. These new monographs and changes will be published in the first supplement to the fourth edition of the Food Chemicals Codex, which is scheduled for publication in late summer, 1997. Copies of the proposed new monographs and revisions to current monographs may be obtained upon written request from NAS (address above) or from the Dockets Management Branch (HFA-305), Food and Drug Administration, 1220 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Requests for copies should specify the monographs desired by name. New and revised monographs may also be obtained through the Internet at http://www2.nas.gov/codex.

FOR FURTHER INFORMATION CONTACT:

SUPPLEMENTARY INFORMATION: By contract with NAS/ICM, FDA supports the preparation of the Food Chemicals Codex, a compendium of specification monographs for substances used as food ingredients. Before any specifications are included in a Food Chemicals Codex publication, public announcement is made in the Federal Register. All interested parties are invited to comment and to make suggestions for consideration. Suggestions should be accompanied by supporting data or other documentation to facilitate and expedite review by the committee.

In the Federal Register of May 31, 1995 (60 FR 31413), FDA last announced that the committee was considering an additional monograph and a number of monograph revisions for inclusion in the fourth edition of the Food Chemicals Codex. The fourth edition of the Food Chemicals Codex was released by the National Academy Press (NAP) in March 1996. It is now available for sale from NAP (1-900-624-6242; 202-334-3131; FAX 202-334-2431; Internet http://www.nap.edu) 2101 Constitution Ave. NW., Lockbox 285, Washington, DC 20035.

FDA now gives notice that the committee is soliciting comments and information on additional proposed new monographs and proposed changes to certain current monographs. These new monographs and changes will be published in the first supplement to the fourth edition of the Food Chemicals Codex, which is scheduled for publication in late summer, 1997. Copies of the proposed new monographs and revisions to current monographs may be obtained upon written request from NAS at the address listed above or through the Internet at http://www2.nas.gov/codex.

FDA emphasizes, however, that it will not consider adopting and incorporating any of the committee’s new monographs or monograph revisions into FDA regulations without ample opportunity for public comment. If FDA decides to propose the adoption of new monographs and changes that have received final approval of the committee, it will announce its intention and provide an opportunity for public comment in the Federal Register.

The committee invites comments and suggestions by all interested parties on specifications to be included in the proposed new monographs (12) and revisions of current monographs (22) that follow:

I. Proposed New Monographs
Beta-Cyclodextrin
Calcium Lignosulfonate
Dimethyl D-carboxyl Glutaric Palmitostearate
4-Flavonesorcinol
Sodium Lignosulfonate
Sucrose Fatty Acid Esters
Sugar Beet Fiber
Reduced Lactose Whey
Reduced Minerals Whey, Whey Protein Concentrate
Autolysed Yeast

II. Current Monographs to Which the Committee Proposes to Make Revisions
Aspartame (delete transmittance test)
Calcium Phosphate, Dibasic (decrease lead limit)
Calcium Phosphate, Monobasic (decrease lead limit)
Calcium Phosphate, Tribasic (decrease lead limit)
Calcium Silicate (revise fluoride test)
Calcium Oxalate (combine nitric oxide and nitrogen dioxide limits, and revise test)
Dextrin (add sulfur dioxide test)
Dietary Sodium Sulfosuccinate (revise identification test)
Enzymes-Methylated Fats (modify enzyme-modified milk monograph)
L-Glutamic Acid (revise identification test 3)
Kojac Flour (revise identification test B)
Magnesium Phosphate, Dibasic (decrease loss on ignition limits)
Nicin (revise identification tests)
Nicotinamide (revise identification tests, assay)
Pectins (revise identification tests)
Potassium Phosphate, Dibasic (decrease lead limit)
Potassium Phosphate, Monobasic (decrease lead limit)
Sodium Acid Pyrophosphate (revise assay limit)
Sodium Carboxymethylcellulose (change primary name to Cellulose Gel)
Sodium Tripolyphosphate (reduce lead limit)
Spice Oleoresins (add oleoresin rosemary)

Whey

Interested persons may, on or before February 18, 1997, submit to NAS written comments regarding the monographs listed in this notice. Timely submission will ensure that comments are considered for the first supplement to the Fourth Edition of the Food Chemicals Codex. Comments received after this date may not be considered for the first supplement, but will be considered for subsequent supplements. Those wishing to make comments are encouraged to submit supporting data and documentation with their comments. Two copies of any comment regarding the monographs listed in this notice are to be submitted to NAS (address above). Comments and supporting data or documentation are to be identified with the docket number found in brackets in the heading of this document and each submission should include the statement that it is in response to this Federal Register notice. NAS will forward a copy of each comment to the Dockets Management Branch (address above). Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m. Monday through Friday.

Dated: November 14, 1996.
Fred R. Shank.
Director, Center for Food Safety and Applied Nutrition.
[FR Doc. 96-31077 Filed 12-2-96; 3:45 am]
BILLING CODE 4160-01-F

[Docket No. 94N-215] DE/1979

Cyclospasmol®; Final Decision on Proposed Withdrawal of Approval of New Drug Application

AGENCY: Food and Drug Administration

ACTION: Notice.
SUMMARY: The Food and Drug Administration (FDA) is announcing that the Commissioner of Food and Drugs (the Commissioner) is issuing his Final Decision on the proposal to withdraw approval of the new drug application (NDA) for the human drug product Cyclospasmol® (cyclandelate) (NDA 11–544). This drug is labeled for use in two indications: specifically, as a treatment for intermittent claudication caused by arteriosclerosis obliterans and as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multiinfarct or Alzheimer's type. The Commissioner has determined that Cyclospasmol® has not been shown to be effective for such uses, and the Commissioner hereby withdraws approval for this drug. The Commissioner's Decision sustains the Final Decision of the Administrative Law Judge (ALJ) who found that Cyclospasmol® had not been shown by sufficient evidence of adequate and well-controlled studies to be effective for its intended uses.


ADDRESSES: The transcript of the hearing, evidence submitted, and all other documents cited in this decision may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 1234 Parklawn Drive, rm. 1–23, Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Nancy E. Pirt, Office of Health Affairs (HFY–1), Food and Drug Administration, 3600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: The purpose of this proceeding has been to determine whether FDA should withdraw approval of the NDA for the human drug product Cyclospasmol® (cyclandelate). This drug is being offered for use in two indications, specifically: (1) As a treatment for intermittent claudication caused by arteriosclerosis obliterans (AHP Exceptions at 14; AHP Post-Hearing Brief at (1)), and (2) as a treatment for cognitive dysfunction in patients suffering from senile dementia of the multiinfarct or Alzheimer's type. (AHP Exceptions at 111; AHP Post-Hearing Brief at 1.)

Under § 12.130 (21 CFR 12.130), the Commissioner makes the following decision adjudicating the significant issues raised by the parties following the administrative hearing. The effect of this decision is that this drug may no longer be marketed in the United States.

Because the Commissioner's discussion of the issues is necessarily detailed, an outline of this discussion is being given for the reader's convenience:

I. The Commissioner's Final Decision
A. Background
B. The Legal Standard
C. The Intermittent Claudication Indication
   1. The MDS–96 (Reich) Study
      a. Objective of the Study
      b. Test of Presence of Disease
      c. Foot Pedal Ergometer as an Evaluative Measure
   2. The Winsor Study
      a. Adequacy of the MDS–96 (Reich) Study
   3. The Five-Center Study
      a. Reanalysis of the Five-Center Study
      b. Inclusion/Exclusion Decisions
      c. Calculation of Treadmill Distances
      d. Variability Among Centers
   4. Adequacy of the Five-Center Study
D. The Senile Dementia Disease Indication
   1. The Rao Study
      a. Admissibility of the Reanalysis
      b. Labeling and Patient Selection
      c. Concomitant Diseases and Conditions
      d. Concomitant Medications
   2. The Yasevage Study
      a. Selection of Patients for the Study
      b. Distribution of Patients with Strokes
      c. Baseline Comparability
      d. Concomitant Medications
      e. Small Sample Size
      f. Clinical Significance
   g. Multiple Tests
   h. Adequacy of the Yasevage Study
II. Conclusion and Order

I. The Commissioner's Final Decision
A. Background
Cyclospasmol® is a drug consisting of 200 milligrams (mg) of cyclandelate. (G–33.2 at 7.) The NDA for Cyclospasmol® (NDA 11–544) was approved at a time when the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) (the act) required only proof of safety. In 1962, the act was amended by the Drug Amendments Act of 1962 (Pub. L. 87–781) to provide that drugs could no longer be approved unless both safety and efficacy had been proved.

The act, as amended, also required FDA to evaluate drugs approved before 1962 to determine whether such drugs were effective and to withdraw approval for any NDA where "substantial evidence" of the drug's effectiveness was lacking. (Section 505(e)(3) of the act (21 U.S.C. 355(e)(3)).) FDA's review of the NDA for Cyclospasmol® revealed that the drug was known as the Drug Efficacy Study Implementation (DESI) program. The act placed the burden of coming forward with evidence of effectiveness on the manufacturer of the drug. (Weinberger v. Hynson, Westcott and Dunning, 412 U.S. 609, 817 (1973), citing 21 U.S.C. 355(g)(1).)

The Commissioner announced in a notice published in the Federal Register of July 20, 1971 (36 FR 13347), that he had evaluated a report received from the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group pertaining to certain peripheral vasodilators for oral use, including Cyclospasmol® Capsules and Tablets. Under the NAS/NRC report, the Commissioner classified Cyclospasmol® as possibly effective for its labeled indications, except for those claims specifically found in the notice to lack substantial evidence of effectiveness.

In a notice published in the Federal Register of December 14, 1972 (37 FR 26623), the FDA announced that it would permit Cyclospasmol® capsules and tablets, as well as other peripheral vasodilators, to remain on the market beyond the time limits prescribed for implementation of the DESI program. In a subsequent notice published in the Federal Register of July 11, 1973 (38 FR 18477), FDA required that by September 10, 1973, persons interested in conducting clinical studies to determine the effectiveness of peripheral vasodilators to submit protocols and provide the agency with notice of the date when such studies were expected to begin.

On June 20, 1978, the manufacturer of Cyclospasmol®, Ives Laboratories, a wholly owned subsidiary of American Home Products (hereinafter referred to as "AHP"), submitted to FDA's Bureau of Drugs (currently the Center for Drug Evaluation and Research (hereinafter referred to as "the Center")), a status report of five completed studies for peripheral vascular disease and five completed studies for cerebral vascular disease studies. These studies were reviewed by the Center and found not to provide substantial evidence of adequate and well-controlled studies indicating the effectiveness of Cyclospasmol® for its labeled indications. In two subsequent notices published in the Federal Register of May 25, 1979 (44 FR 30436; 44 FR 30442), FDA proposed to withdraw approval for Cyclospasmol®'s NDA and offered an opportunity for a hearing on the proposed withdrawal. Ives Laboratories (hereinafter referred to as AHP) was also given until May 26, 1980, to complete any studies which were still in progress.

On October 18, 1984 (49 FR 40572), Under
21 CFR 12.45, both the Center and AHP filed notices of participation. A prehearing conference was held on January 15, 1985. Following the submission of written testimony and documentary evidence, a hearing was held before ALJ Daniel J. Davidson beginning on June 18, 1985, and ending on June 27, 1985.

Subsequently, on September 25, 1986, Judge Davidson issued his decision, in which he found that the efficacy of Cyclospasmol had not been proved by substantial evidence of adequacy and well-controlled clinical trials, and that the conclusion of NDA 11-544 should be withdrawn. Both AHP and the Center filed exceptions to various points in Judge Davidson's decision and appealed to the Commissioner, under 21 CFR 12.125.

B. The Legal Standard

I am issuing this Final Decision under § 12.130. In taking this action, I have all the powers I would have had in making the Initial Decision. (§ 12.130(a); see also Commissioner's Decision on Polychlorinated Biphenyls (49 FR 21514 at 21519, May 22, 1984).) Further, under § 5.10 (21 CFR 5.10(a)(1)), I have been delegated the authority by the Secretary of the Department of Health and Human Services "to determine, after giving full consideration to all of the evidence that has been submitted, including expert opinions, if the [evidence] meet[s] the regulatory criteria and show[s] effectiveness." (Warner-Lambert Co. v. Heckler, 787 F.2d 147, 154 (3d Cir. 1986).)

In the present case, I have fully reviewed the complete administrative record: (1) the transcript of the hearing that was held before the ALJ from June 18, to June 27, 1985; (2) the written testimony and documentary evidence submitted by AHP and the Center before, during, and after the Hearing; (3) the exceptions which AHP and the Center filed to the ALJ’s Decision; and (4) all briefs filed by AHP and the Center pursuant to this matter.

My Decision is based upon a full review of the facts and arguments that appear in the record, and my independent conclusions are based upon that review.

AHP first argues that the ALJ’s decision did not meet the minimum standard required by the Administrative Procedure Act and, by FDA regulations, pertaining to initial decisions following formal adjudicatory proceedings. (AHP Exceptions at 3, citing 5 U.S.C. 557(c) and 21 CFR 12.120(b).) In support of its argument, AHP cites the Administrative Procedure Act for the requirement that all initial decisions shall include a statement of “findings and conclusions, and the reasons or basis therefor, on all the material issues of fact, law, or discretion presented on the record.” (AHP Exceptions at 3, quoting 5 U.S.C. 557(c).) AHP also cites FDA regulations, which state that initial decisions contain findings of fact based upon relevant, material and reliable evidence in the record and also contain “(a) discussion of the reasons for the findings and conclusions, including a discussion of the significant contentions made by any participant” with “(c)itations to the record supporting the findings and conclusions.” (AHP Exceptions at 3, quoting 21 CFR 12.120(b).)

AHP argues that the ALJ did not state how he arrived at his findings of fact. (AHP Exceptions at 8.) Ignoring the bulk of the ALJ’s decision, AHP refers to the conclusion section of the ALJ’s decision, which is appropriately entitled “Conclusions,” to argue that the ALJ simply announced his findings in one sentence decree. (AHP Exceptions at 9, citing the ALJ’s Initial Decision (I.D.) at 23.)

In this critical issue was addressed in the Commissioner’s Decision on Lutrexin, wherein the Commissioner stated:

(The manufacturer) implies that the findings and order are deficient because the numbered findings of fact at the end of the narrative do not contain the evidentiary details that (the manufacturer) feels would justify the judge’s ruling. Those details, however, are fully set out in the judge’s narrative explanation. Stating, discussing, and resolving factual issues in narrative form rather than in numbered paragraphs is a commonly used format that has been specifically recognized as fulfilling the Administrative Procedure Act requirement of a “statement of * * * findings and conclusions * * * on all the material issues of fact, law, or discretion.” 5 U.S.C. 557(c).

Gilbert Middle Co. v. United States, 355 U.S. 557 (1958). The Commissioner’s Decision on Oral Proteolytic Enzymes (OPE), it was held that, except in certain limited cases, a minimum of two adequate and well-controlled studies are required. (Commissioner’s Decision on OPE, slip op. at 23; FDA Docket No. 79N-0139 (FDA May 30, 1985), aff’d sub nom. on other grounds Warner-Lambert Co. v. Heckler, 787 F.2d 147 (3d Cir. 1986).) This requirement arises from the statutory language of the act at 21 U.S.C. 355(d), which mandates the submission of a plural number of adequate and well-controlled investigations.

Commissioner’s Decision on OPE, slip op. at 23; Commissioner’s Decision on Depro[58 FR 50929 at 50936, September 29, 1993.]

FDA has permitted exceptions to the requirement for at least two adequate and well-controlled studies in limited circumstances, including: (1) When the disease is very rare and it is extremely difficult to obtain enough subjects for two studies, (2) when the disease process is expensive to study experimentally, (3) when the study conducted is very large and multicentered, and (4) when the disease is rapidly fatal and there is no alternative therapy. (Commissioner’s Decision on OPE, slip op. at 24; Commissioner’s Decision on Deprol, 58 FR 50929 at 50936.) AHP does not argue that any of these exceptions apply to the present case, nor do I find these exceptions to be applicable. Therefore, I find no merit in AHP’s objections to the ALJ’s rulings that at least two adequate and well-controlled studies are necessary to demonstrate the efficacy of Cyclospasmol.

Finally, AHP argues that many sections of the ALJ’s Decision are paraphrase, or contain recitations of portions of the post-hearing briefs filed by the Center and AHP. AHP states that, as a result, “[t]he substantive statements made by the ALJ raise questions as to the ALJ’s understanding of the issues.” (AHP Exceptions at 12.) AHP has not cited, however, any authority which indicates that it is impermissible for an ALJ to paraphrase or recite in his decision statements from the post-hearing briefs. After reviewing the ALJ’s Decision, I find that the ALJ fully set out the reasons for the conclusions he reached. Additionally, I find that AHP’s claim that “[t]he ALJ’s Decision fails to...
made in the Yesavage study. I find the Center’s arguments to have merit.

A comparable issue was adjudicated in the Commissioner’s Decision on
Mystecin. Therein, it was ruled, “(E)ven if the subgroups and multiple
endpoints had been identified in the protocol, * * * some downward
adjustments in the p values should have been made to correct for the analyses
of multiple subgroups and endpoints.”

In Commissioner’s Decision on Mystecin, slip op. at 43; see also Commissioner’s
Decision on Deprol, 58 FR 50929 at
50933.) Similarly, in the
Commissioner’s Decision on Deprol, it was noted that, “(i) Although
pair-wise comparisons are made, some
comparisons will be statistically
significant by chance alone.”

Can Commissioner’s Decision on Deprol, 58
FR 50929 at 50933.) When multiple
comparisons are made, corrections in the p values are needed to maintain the
correct Type I error rate because the
likelihood of a Type I error increases
with the number of individual
comparisons. (Commissioner’s Decision
on Deprol, 58 FR 50929 at 50933.) In other
words, as one great author more
expressively observed, “Fortune brings
in some boats that are not steered.”

Shakespeare, Cymbeline, IV, iii, 45.)

For these reasons, I find that in
weighing the adequacy of the Yesavage
study, it is proper to consider the fact
that numerous statistical analyses were
employed, and to consider that the
particular outcome of interest was not
specified in advance, nor were
adjustments to the p value made.

Accordingly, I find no error in the ALJ’s
ruling on this point.

II. Adequacy of the Yesavage Study

In sum, I find that the Yesavage study was
not adequate and well-controlled. In
making this determination, I have
considered the aggregate effect of the
protocol violations. I base my ruling
upon these findings: (1) That the
selection of patients for the study was
flawed by the inclusion of patients with
the concomitant condition of
Parkinson’s disease, and by the
inclusion of outpatients, who were to be
excluded under the protocol; (2) That the
failure to show that stroke patients were
included in both the drug and the
placebo arms of the clinical trial can be
considered as a flaw in the study; (3)
That the fact that a statistically
significant difference between test and
control groups existed on the BMT was
a proper consideration; (4) That the
uncontrolled use of concomitant
medication and the poor documentation
of concomitant medication use weighs
against finding the Yesavage study to be
adequate and well-controlled; (5) That
the small sample size was a proper
factor to be considered in reviewing the
results of the study, and can be weighed
against the adequacy of the study; (6)
That the improvement of patients on
SCAG Factor 1 was not clinically
significant; and (7) That the fact that
numerous statistical analyses were
employed and that the particular
outcome of interest was not specified in
advance, nor were adjustments to the p
value made, can be weighed against the
adequacy of the study.

II. Conclusion and Order

The foregoing opinion in its entirety
constitutes my findings of fact and
conclusions of law. Based on the
foregoing discussion, findings, and
conclusions, I affirm the ALJ’s Initial
Decision in all respects, except where
specifically stated otherwise. I find that
there is a lack of substantial evidence
that Cyclospasmol® will have the effect
it purports or is represented to have under the conditions of use prescribed,
recommended, or suggested in its
labeling. Accordingly, under 21 U.S.C.
355(e)(3), the NDA for Cyclospasmol®
must be withdrawn. I further find that,
by reason of the lack of substantial
evidence of its effectiveness,
Cyclospasmol® is a “new drug” within
the meaning of 21 U.S.C. 321(p).

Therefore, under the Federal Food,
Drug, and Cosmetic Act, 21 U.S.C.
355(e), and under authority delegated to
me by the Secretary (§ 5.10(a)(1)), the
new drug application for Cyclospasmol®
and all amendments and supplements thereto, are hereby withdrawn, effective

Dated: November 12, 1996.

Michael A. Friedman,
Deputy Commissioner for Operations.

Procedures for Issuance of and Review
and Response to Materials Submitted
In Response to Clinical Hold Letters
for Investigational New Drug (IND)
Applications; Availability

AGENCY: Food and Drug Administration,
HHS.

ACTION: Notice.

SUMMARY: The Food and Drug
Administration (FDA) is announcing the
availability of two documents entitled
“Centerwide Policy on Issuance of and
Response to Clinical Hold Letters for
Investigational New Drug Applications
(CD-2–96)-Center for Biologics Evaluation and Research (CBER) and
IND Process and Review Procedures”
(MAPP 6030.1, Center for Drug
Evaluation and Research (CDER)). The
documents specify the procedures for
the issuance of and review and response to
material submitted in response to a
notice of clinical hold. It is intended
that these documents will clarify the
agency’s policy in regard to responses to
clinical holds. The documents are made
available as part of the agency’s
commitment to review and respond to
data submitted in response to a clinical
hold within 30 days of receiving the
submission, as stated in the November
1995, Presidential National Performance
Review report entitled “Reinventing the
Regulation of Drugs Made from
Biotechnology.”

ADDRESSES:
CDER Information: For additional
copies of the documents submit
written requests to the
Manufacturers Assistance and
Communications Staff (HPM-42),
Center for Biologics Evaluation
and Research (CBER), Food and Drug
Administration, 1401 Rockville
Pike, Rockville, MD 20852-1448.

For additional copies of the
documents, contact the
CDER Information:
[phone number]

CDER Information: For additional
copies of the documents contact the
Drug Information Branch (HFD–
210), Division of Communications
Management, Center for Drug
Evaluation and Research (CDER),
Food and Drug Administration,
5600 Fishers Lane, Rockville, MD
20857, 301–594–1012. The form
may also be obtained by calling the
CDER FAX Information System at
1–888–CDER FAX, or 301–827–3844.

For additional copies of the
documents, contact the
CDER Information:
[telephone number]

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For additional copies of the
documents, contact the
CDER Information:
[telephone number]
CYCLANDELATE

LD50 is greater than 2 g/kg.

It has produced ataxia, altered sleep, flushing, headache, tachycardia.
CYCLANDELATE (Cyclospasmol®)


REFERENCES


## HYRDAZINE SULFATE
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**FDA Review/Recommendation**

**Background Information**

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Hydrazine sulfate is a chemical compound that inhibits gluconeogenesis in animals. As a result of this property, since the mid 1970s, it has been used by numerous investigators in patients with different cancers in attempts to improve their underlying condition.

Chemically this compound has been properly characterized and has proven to be stable.

Initially, as commonly happens in clinical research, reports of open label uncontrolled studies with hydrazine sulfate were published claiming efficacy in improving patients' well being, survival, and weight gain in cancers of diverse organs. Moreover, the papers suggested that patients were able to tolerate hydrazine quite well and that its side effects were characterized as mild.

Of particular importance in this chain of events was the publication of Dr. Gold (Oncology 32:1, 1975) where in an open label study he reported the outcome of 84 cancer patients of the original 158 studied, claiming efficacy. This study lead to the design of new studies and to numerous requests for the compassionate use of Hydrazine. The Division granted all these requests as well as supported the initiation of well-designed studies. Among these, some studies are worth citing.

Chlebowski et al (J. Clin Oncol, 8:9, 1980) studied 65 patients with Non-Small Cell Lung Cancer. Patients randomized to Hydrazine plus chemotherapy had significant greater caloric intake and albumin maintenance that those receiving only chemotherapy. Survival, as well as body weight, or objective tumor responses, however, did not differ between groups. A subgroup analysis showed survival improvement in the cohort with less advanced cancer receiving hydrazine. It is not known, however, whether this analysis was prospectively designed or performed post hoc. There are no references to toxicity in this paper.

Based on these initial results, the National Cancer Institute sponsored three randomized controlled studies involving in excess of 600 patients similar to those studied by Chlebowski as well as others with advanced colorectal cancer. End points included survival, weight and QOL. None of these studies provided the desired outcomes. (J. Clin Oncol 12:1113, 1121, and 1126, 1994.)
It is worth mentioning that these new studies were not able to replicate favorable outcomes either in albumin levels or QOL, and that these parameters were better in the placebo treated group. In contrast to Chlebowski’s report, patients with less advanced cancer staging did not benefit from the addition of Hydrazine in respect to physical functioning, fatigue, cancer related symptoms, overall QOL and suffered more neurotoxicity than those receiving placebo.

In addition, one of the studies was terminated prematurely because of worsening of median survival in patients randomized to hydrazine. Furthermore, these studies encompassed patients both receiving chemotherapy or not, and in neither group did hydrazine show benefit.

As a result of all these unfavorable outcomes the NCI discontinued support for this line of research. The Division concluded that patients receiving Hydrazine were at greater risk of death and complications than those not exposed to this drug. The decision, based upon the results of all well designed studies, was not to grant more compassionate INDs for hydrazine (July 20, 1994.)

Supporters of Hydrazine complained that the randomized controlled studies differed from the original positive studies in that patients in the NCI’s sponsored studies were allowed to receive, in addition to hydrazine, tranquilizers, barbiturates, and alcohol. All these substances were not used in Gold’s study and are believed to potentially diminish hydrazine therapeutic properties. The General Accounting Office examined these complaints and found them to be without merit.

In summary, when properly tested, Hydrazine has not proven effective in patients with small cell lung carcinoma and in patients with colorectal cancer. Moreover, Hydrazine may worsen outcomes of patients with these conditions by reducing life expectancy, quality of life and by inducing untoward adverse reactions.
MEMORANDUM-TO-THE-FILE

IND 35/458
Randall, A., Oen, M.D.,
Hydrazine sulfate

A meeting was held with Dr. Sobel, Dr. Parish, and myself in attendance. After discussing the lack of demonstrated efficacy in the NIH clinical trials regarding hydrazine sulfate with Dr. Parish, Dr. Sobel decided that compassionate INDs for hydrazine sulfate will no longer be issued and all INDs for hydrazine sulfate in the division will be terminated.

Stephen Troostle

Stephen Troostle
CSO-DMEDP

cc: IND Arch
    HFD-510
    HFD-510/S-Trostle \HS.MEM

July 20, 1994