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 2 - Use of SADBE in Human Papillomavirus Infection

Author	Journal	Year	Disease	N	Treatment	Response/ITT
Paller et al.	AAD Academy Summer Meeting	1998	Verruca vulgaris in children	61	Sensitize 2% Treat 2-3X/wk c initial 0.2%	58% complete clearance p average of 7 wks
Iijima et al.	Dermatology	1993	Verruca vulgaris	20	Sensitize 2% Treat q week 0.1 or 0.01 %	60% after avg of 6 applications

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 diphencyprone [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 that 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

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

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

Reference	Disease	Treatment of Choice	Other Suggested Treatments	Role of SADBE in Therapeutic Armamentarium
Andrews' Diseases of the Skin: Clinical Dermatology, ed. by Arnold et al., Eighth edition (1990) (textbook)	Alopecia Areata—patchy involvement	Intralesional injections of corticosteroid	"None of the other various therapeutic approaches are clearly superior to corticosteroids"	SADBE: not discussed
	Alopecia Areata—totalis/universalis	Systemic (IM) steroids should be "seriously considered".		
	Common/ Plantar Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K (not plantar warts), L, M	"It (SADBE) may be worth trying in very large and resistant warts."
Dermatology in General Medicine, ed. by Fitzpatrick et al., Third edition (1987) (textbook)	Alopecia Areata	Treatment of choice not identified	N (little efficacy), P, Q, R	"SADBE (nonmutagenic)...used successfully"; "local discomfort is a problem"
	Warts	Treatment of choice not identified	A, B, C, D, E, F, G, H, I, J, K, T, U, V	SADBE: may be suitable substitute, because it is negative in the Ames mutagenicity assay
Textbook of Dermatology, ed. by Rook et al., Fourth Edition (1986) (textbook)	Alopecia Areata	Treatment of choice not identified	O (unclear if regrowth is maintained), P (not helpful in alopecia totalis—except for eyebrows), W, X, Y, Z	Possible teratogenicity of DNCB (another topical sensitizer) led to SADBE substitution
	Warts	Treatment of choice not identified	B, C, D, L, L', E, H, I, J, T, A', B', ; avoid A,U (risk of scarring)	SADBE: not mentioned
Pediatric Dermatology, ed. by Schachner and Hansen, (1988) (textbook)	Alopecia Areata	Topical corticosteroids, alone or under occlusion; Intralesional corticosteroids	O (for severe involvement, unresponsive to topical or intralesional treatment)	SADBE: as effective as DNCB. "[SADBE] cannot be regarded as completely safe until extensive toxicologic evaluation has been completed."
	Warts	Treatment of choice not identified	A, B, C, G, K	

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**: Intralesional 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 pigmentary and eczematous reactions).

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DMINOPYRIDINES

Table of Contents

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.

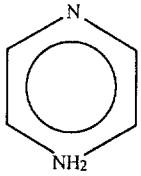
A literature review, ignoring drug overdoses, revealed 3 seizures for diaminopyridine and 6 for 4-aminopyridine. There is a suggestion from the literature that seizures with 4-aminopyridine have occurred at the lower dose range (35 mg/day) while those with diaminopyridine have been at the highest dose 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:	$C_5H_6N_2$
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.

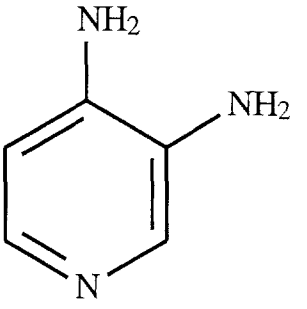
Analytical Chemistry

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:	$C_5H_7N_3$
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

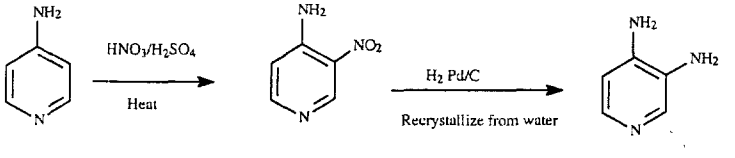
3,4-DAP was first prepared as a synthesis intermediate by O. Bremer in 1935, Clark-Lewis, et al. in 1962, and Campbell, et al. in 1986 by different methods. This material is commercially available. It has been has been well characterized. It is stored in tight light-resistant containers to maintain its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

1. Potter, Hayes, Segal, et al. Randomized double-blind crossover trial of fampridine-SR in patients with incomplete spinal cord injury. J Neurotrauma 1998 Oct;15(10): 837-49.

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)

1. van Diemen, Polman, et al. The effect of 4 aminopyridine on clinical signs in MS: A randomized, placebo-controlled, double-blind, cross-over study. Ann Neurol 1992; 32:123-130.

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 pro-convulsant 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

1. Bever, Anderson, Leslie, et al. Treatment with oral 3,4-diaminopyridine improves leg strength in multiple sclerosis patients: results of a randomized, double-blind, placebo-controlled, crossover trial. Neurology 1996; 47: 1457-1462.

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 1-20mg capsule/day up to 5-20mg capsules/day over 5 days.

22 pts improved on DAP; 2 pts improved on placebo. Secondary measures 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)

1. McEvoy, Windebank, Daube, and Low. 3,4-diaminopyridine in the treatment of Lambert-Eaton Myasthenic Syndrome. NEJM 1989;321: 1567-71.

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

2. Sanders. 3,4-diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. Ann NY Acad Sci 1998 May 13; 841: 811-6.

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

Szmanda and Bryant Neurology

2200 Oriole Lane, Suite #1, Wausau, Wisconsin 54401
Phone 715-845-4400 800-845-4844 Fax 715-848-9375

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 trail 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

[redacted]

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

Pharmacy Compounding Advisory Committee

May 6-7, 1999
Advisory Committee Conference Room, 1066
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5630 Fishers Lane
Rockville, MD 20852

Background Materials

Table of Contents

Volume 3

Drug Substances Nominated for the Bulks List

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

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%

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[1] Ophthalmic Drug Facts. Facts and Comparisons, St. Louis, MO. 1992. pp.106-107.

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.[2] 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.[3] The silver deposits in the cornea are located in Descemet's membrane[3] and may occur with clinical conjunctival involvement.[4] In the lacrimal sac, the silver is deposited in the mucosal epithelium.[5] In the lens, it may cause anterior subcapsular discoloration or in the nucleus.[6]

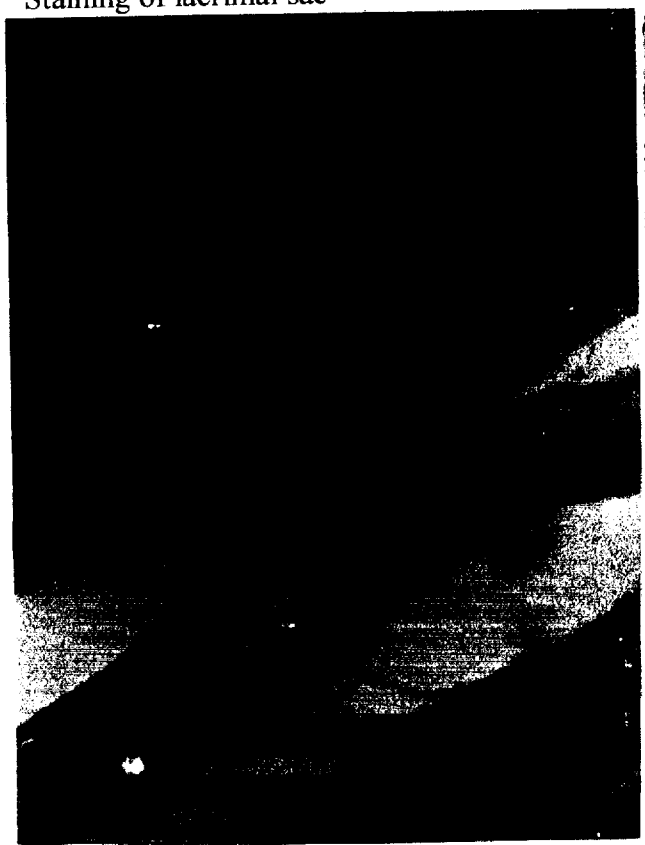
Most reported cases of argyrosis have occurred following at least 2 months of instillation,[7] however, Karcioglu and Caldwell reported a case of ocular argyrosis after only one treatment with Argyrol eye drops.[8] The conjunctival, corneal and lens manifestations are shown below.[3,9]

Argyrosis is generally permanent and although not usually known to impair visual acuity, has been associated with decreased night vision[10]. Decreased night vision has been correlated with increased levels of silver in both the conjunctiva and the cornea.

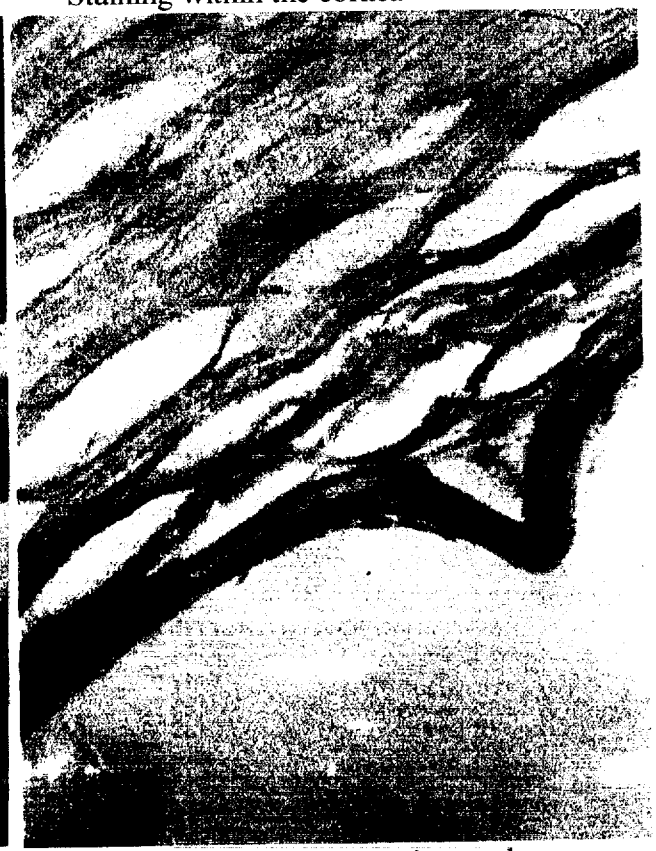
[3] Hanna C, Fraunfelder FT, Sanchez J. Ultrastructural Study of Argyrosis of the Cornea and Conjunctiva. *Arch Ophthalmol.* 1974;92:18-22.
[4] Gutman FA, Crosswell HH. Argyrosis of the Cornea with Clinical Conjunctival Involvement. *Am J Ophthalmol.* 1968;65:183-4.
[5] Yanoff M, Scheie HG. Argyrosis of the Conjunctiva and Lacrimal Sac. *Arch Ophthalmol.* 1964;72:57-8.
[6] Bartlett RE. Generalized Argyrosis with Lens Involvement. *Am J Ophthalmol.* 1954;38:402-3.
[7] Loeffler KU, Lee WR. Argyrosis of the lacrimal sac. *Graefes Arch Clin Exp Ophthalmol.* 1987;225(2):146-50.
[8] Karcioglu ZA, Caldwell DR. Corneal argyrosis: histologic, ultrastructural and microanalytic study. *Can J Ophthalmol.* 1985 Dec;20(7):257-60.
[9] The Cornea. Gilbert Smolin and Richard Thoft editors. Little, Brown and Company. Boston 1983. p. 386.
[10] Moss AP, *et al.* The Ocular Manifestations and Functional Effects of Occupational Argyrosis. *Arch Ophthalmol* 1979;97:906-908.

Staining of lacrimal sac

Staining within the cornea



Silver impregnation of epithelial basement membrane[11]



Involvement of Descemet's membrane

[11] Diseases of the Cornea. 2nd Edition. Merrill Grayson editor. C.V. Mosby Co. St. Louis 1983. pp. 576-578.

Efficacy

***In vitro* Studies**

1. Thompson R, Isaacs ML, Khorazo D. *Am J Ophthalmol* 20:1087, 1937 copied with permission in Havener's Ocular Pharmacology. 6th edition. Mosby 1994.

Bacterial Effect of Nonirritating Concentrations of Antiseptics

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

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

2. Peeters M, Vanden Berghe D, Meheus A. Antimicrobial activity of seven metallic compounds against penicillinase producing and non-penicillinase producing strains of Neisseria gonorrhoeae. *Genitourin Med* 1986 Jun;62(3):163-5.

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.

	MIC90 Concentration at which 90% of all strains were inhibited (mg/L)
Phenylmercuric borate	5
Thiomersal	5
Mercuric chloride	20
Silver nitrate	80
Mild silver protein	**200**

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

Controlled Clinical Studies

3. **Isenberg S, Apt L, Yoshimuri R. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Arch Ophthalmol* 1983;101(5):764-5.**

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.

		Mean ± SD	
		Before preparation	After preparation
Colonies	Untreated	183 ± 425	284 ± 571
	Mild silver protein	**231 ± 687**	**323 ± 750**
Species	Untreated	1.06 ± .83	1.41 ± .86
	Mild silver protein	**1.06 ± .75**	**1.31 ± .77**
Number of Eyes in which Culture was Sterile	Untreated	8	4
	Mild silver protein	**7**	**5**

"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.*

4. **Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical povidone-iodine. *Ophthalmology* 1991 Dec;98(12):1769-75.**

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[12]

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.

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[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[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[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 nitroersol (Metaphen), 1:2,500 thimerosal (Merthiolate), and 1:5,000 mercuric oxycyanide."

"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."

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[13] Goodman and Gilman's The Pharmacological Basis of Therapeutics. 6th Edition. MacMillan Publishing Co., Inc. New York. pp. 977.

[14] Havener's Ocular Pharmacology. 6th Edition. Mosby. New York. pp. 239, 463-4, 475-6, 484-7.

A. INGREDIENT NAME:

SILVER PROTEIN MILD NF

B. Chemical Name:

C. Common Name:

Argentum Crede, Collargol (9CI), Colloidal Silver, Stillargol, Vitargénol, Aust.: Coldargan, Fr.: Pastaba, Ger.: Coldargan, Ital.: Arscolloid, Bio-Arscolloid, Corti-Ascolloid, Rikosilver, Rinatipiol, Rinovit Nube.

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

	(Specifications)	*(Results)*
Assay: (after ignition)	19.0-23.0%	19.74%

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:

Isenberg, S., Apt, L., and Yoshimuri. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Archives of Opthalmology,* 1983; 101(5): 764-765.

Apt, L. and Isenberg, S. Chemical preparation of skin and eye in ophthalmic surgery: an international survey. *Opthalmic Surgery,* 1982; 13(12): 1026-1029.

H. Information about dosage forms used:

Liquid

I. Information about strength:

1-20%

J. Information about route of administration:

Nasal
Opthalmic

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1263
51149

PRODUCT: SILVER PROTEIN MILD
RELEASE #: N

LOT # :B61695G18

GRADE:NFXIII
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) D	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 A

MANUFACTURE LOT NO.: C64051D10

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
E { 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.:** _____

Sesame Oil (7368-w)

Aceite de Ajonjolí; Benne Oil; Gingelly Oil; Oleum Sesami; Teel Oil.

Pharmacopoeias. In Aust., Belg., Br., Chin., Eur., Fr., Ger., It., Jpn, Neth., Port., and Swiss. Also in *USNF*.

The standards of Ph. Eur. apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

The fixed oil obtained from the ripe seeds of *Sesamum indicum* (Pedaliaceae) by expression or extraction and subsequent refining. It is a clear pale yellow oil, almost odourless and with a bland taste with a fatty-acid content consisting mainly of linoleic and oleic acids. It solidifies to a buttery mass at about −4°.

Slightly **soluble** to practically insoluble in alcohol; miscible with carbon disulphide, chloroform, ether, and petroleum spirit. Store at a temperature not exceeding 40° in well-filled airtight containers. Protect from light.

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been observed.

Shellac (285-x)

904; Gomme Laque; Lacca; Lacca in Tabulis; Schellack.

Pharmacopoeias. In Fr. and Ger. Also in *USNF*.

Jpn includes Purified Shellac and White Shellac (Bleached).

Shellac is obtained by purification of the resinous secretion of the insect *Laccifer lacca* Kerr (Coccidae). The USNF describes 4 grades: Orange Shellac is produced by filtration in the molten state or by a hot solvent process, or both; removal of the wax produces Dewaxed Orange Shellac; Regular Bleached (White) Shellac is prepared by dissolving the secretion in aqueous sodium carbonate, bleaching with hypochlorite, and precipitating with sulphuric acid; removal of the wax by filtration during the process produces Refined Bleached Shellac.

Practically **insoluble** in water; very slowly soluble in alcohol 85% to 95% (w/w); soluble in ether, 13% to 15%, and in aqueous solutions of ethanolamines, alkalis, and borax. Store preferably at a temperature not exceeding 8°.

Shellac is used as an enteric coating for pills and tablets, but disintegration time has been reported to increase markedly on storage.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USNF 18: Pharmaceutical Glaze.

Siam Benzoin (273-c)

Benjoin du Laos; Benzoe Tonkinensis.

Pharmacopoeias. In Aust., Chin., Fr., It., and Swiss. Also in many pharmacopoeias under the title benzoin and should not be confused with Sumatra Benzoin. Hung., Jpn, and US allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

A balsamic resin from *Styrax tonkinensis* (Styracaceae) and containing not more than 10% of alcohol (90%)-insoluble matter.

Yellowish-brown to rusty brown compressed pebble-like tears with an agreeable, balsamic, vanilla-like odour. The tears are separate or very slightly agglutinated, milky white on fracture, [illegible] and brittle at ordinary temperatures, but soften[illegible]

Sia[illegible] een used similarly to Sumatra benzoin [illegible] een used as a preservative and was formerly [illegible] ration of benzoinated lard.

Prepar[illegible]

Names of pre[illegible] isted below; details are given in Part 3.

Official Prep[illegible]

USP 23: Comp[illegible] Tincture; Podophyllum Resin Topical Solution.

Proprietary Prep[illegible]

Multi-ingredient pre[illegible] s. *Canad.:* Benzoinspray†; Cold Sore Lotion†; *Ital.:* Onds[illegible] *pain:* Vahos Balsamicos†.

Silver (5316-v)

E174.

= 107.8682.

[illegible] 7440-22-4.

Pharmacopoeias. In Swiss.

A pure white, malleable and duc[illegible] l.

Silver possesses antibacterial prop[illegible] nd is used topically either as the metal or as silver salts [illegible] t absorbed to any great extent and the main problem [illegible] ed with the metal is argyria, a general grey discoloration. Silver is used as a colouring agent for some types of confectionery. It is also used as Argentum Metallicum in homoeopathy.

Numerous salts or compounds of silver have been employed for various therapeutic purposes, including silver acetate (p.1751), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganite, silver nitrate (p.1751), silver-nylon polymers, silver protein (p.1751), and silver sulphadiazine (p.273).

A report of reversible neuropathy associated with the absorption of silver from an arthroplasty cement.[1]

1. Vik H, *et al.* Neuropathy caused by silver absorption from arthroplasty cement. *Lancet* 1985; i: 872.

Coating catheters with silver has been reported to reduce the incidence of catheter-associated bacteriuria,[1,2] but other studies have reported increased infection.[3]

1. Lundeberg T. Prevention of catheter-associated urinary-tract infections by use of silver-impregnated catheters. *Lancet* 1986; ii: 1031.
2. Johnson JR, *et al.* Prevention of catheter-associated urinary tract infections with a silver oxide-coated urinary catheter: clinical and microbiologic correlates. *J Infect Dis* 1990; 162: 1145–50.
3. Riley DK, *et al.* A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. *Am J Med* 1995; 98: 349–56.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Austral.: Micropur; *Canad.:* Tabanil; *Ger.:* Dulcargan†; Silargetten†.

Multi-ingredient preparations. *Austral.:* Sima-Varix Bandage†; Simanite†; *Fr.:* Sterilet T au Cuivre Argent†; *Ger.:* Adsorgan†; Grüne Salbe "Schmidt" N; *Ital.:* Actisorb Plus; Agipiù; Katoderm; Katoxyn; Nova-T; Silver-Nova T†; *Spain:* Argentocromo; *UK:* Actisorb Plus.

Silver Acetate (5319-p)

Argenti Acetas.

CH_3COOAg = 166.9.

CAS — 563-63-3.

Pharmacopoeias. In Aust. and Hung.

Silver acetate has been used similarly to silver nitrate as a disinfectant. It has also been used in antismoking preparations.

References.

1. Jensen EJ, *et al.* Serum concentrations and accumulation of silver in skin during three months' treatment with an anti-smoking chewing gum containing silver acetate. *Hum Toxicol* 1988; 7: 535–40.
2. Gourlay SG, McNeill JJ. Antismoking products. *Med J Aust* 1990; 153: 699–707.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

UK: Tabmint.

Silver Nitrate (5321-h)

Argenti Nitras; Nitrato de Plata; Nitrato de Prata.

$AgNO_3$ = 169.9.

CAS — 7761-88-8.

Pharmacopoeias. In Aust., Belg., Br., Cz., Eur., Fr., Ger., Hung., Int., It., Jpn, Neth., Port., Swiss, and US.

The standards of Ph. Eur. apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

Colourless or white transparent crystals or crystalline odourless powder. On exposure to light in the presence of organic matter, silver nitrate becomes grey or greyish-black.

Soluble 1 in 0.4 of water and 1 in 30 of alcohol; its solubility is increased in boiling water or alcohol; slightly soluble in ether. A solution in water has a pH of about 5.5.

Silver nitrate is incompatible with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility. Store in airtight non-metallic containers. Protect from light.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose from the reaction of the silver nitrate with alkali released from the glass bottle which appeared to be soda-glass.[1]

1. *PSGB Lab Report P/80/6* 1980.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, sialorrhoea, diarrhoea, vomiting, coma, and convulsions.

A short lived minor conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness. Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria, which though difficult to treat is considered to be mainly a cosmetic hazard, see under Silver (above).

Absorption of nitrite following reduction of nitrate may cause methaemoglobinaemia. There is also a risk of electrolyte disturbances.

Treatment of these adverse effects is symptomatic.

Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.[1] After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The corneas had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibiotics and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Hornblass A. Silver nitrate ocular damage in newborns. *JAMA* 1975; 231: 245.

Pharmacokinetics

Silver nitrate is not readily absorbed.

Uses and Administration

Silver nitrate possesses disinfectant properties and is used in many countries as a 1% solution for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p.151) when 2 drops are instilled into each conjunctival sac of the neonate. However, as it can cause irritation, other agents are often used.

In stick form it has been used as a caustic to destroy warts and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical disinfectants and astringents in other conditions.

Silver nitrate (Argentum Nitricum; Argent. Nit.) is used in homoeopathic medicine. It is also used in cosmetics to dye eyebrows and eye lashes in a concentration of not more than 4%.

Cystitis. Comment on silver nitrate irrigation having limited value in the management of haemorrhagic cystitis after radiotherapy.[1]

1. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; i: 304–6.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Proprietary Preparations

Austral.: Howe's Solution†; Quit†; *Ger.:* Mova Nitrat; Pluralane; *Spain:* Argenpal.

Multi-ingredient preparations. *Austral.:* Super Banish; *Spain:* Argentofenol; *Switz.:* Grafco; *UK:* AVOCA.

Silver Protein (5322-m)

Albumosesilber; Argentoproteinum; Argentum Proteinicum; Protargolum; Proteinato de Plata; Proteinato de Prata; Strong Protargin; Strong Protein Silver; Strong Silver Protein.

CAS — 9007-35-6 (colloidal silver).

NOTE. Synonyms for mild silver protein include: Argentoproteinum Mite; Argentum Vitellinicum; Mild Protargin; Mild Silver Proteinate; Silver Nucleinate; Silver Vitellin; Vitelinato de Plata and Vitelinato de Prata.

Pharmacopoeias. In Aust., Belg., Cz., Fr., Hung., It., and Jpn. Many of these pharmacopoeias include monographs on mild silver protein as well as on colloidal silver.

Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and have been used as eye drops and for application to mucous membranes. The mild form of silver protein is considered to be less irritating, but less active.

Colloidal silver which is also a preparation of silver in combination with protein has also been used topically for its antibacterial activity.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Sullargol; Vitargénol.

Multi-ingredient preparations. *Aust.:* Coldargan; *Fr.:* Pastaba; *Ger.:* Coldargan†; *Ital.:* Arscolloid; Bio-Arscolloid; Corti-Arscolloid; Rikosilver; Rinantipiol; Rinovit Nube.

Slippery Elm (5458-t)

Elm Bark; Slippery Elm Bark; Ulmus; Ulmus Fulva.

Pharmacopoeias. In US.

The dried inner bark of *Ulmus fulva* (=*U. rubra*) (Ulmaceae).

Slippery elm contains much mucilage and has been used as a demulcent.

Epidermal necrolysis. Based on the treatment of 10 cases, the following was suggested as treatment for toxic epidermal necrolysis: continuous moist compresses of silver nitrate solution 0.25 to 0.5%, with generous wrapping to prevent excessive cooling; daily electrolyte estimations; and daily debridement; after about the fourth day the compresses could be replaced by dexamethasone/neomycin spray followed by inunction of wool alcohols ointment. A penicillin should be given routinely and steroids if vasculitis was present.— P. J. Koblenzer, *Archs Derm.*, 1967, *95*, 608.

Herpes simplex. Silver nitrate 1% had little effect *in vitro* or *in vivo* against herpes simplex virus type 2.— V. R. Coleman *et al.*, *Antimicrob. Ag. Chemother.*, 1973, *4*, 259. A further study.— F. Shimizu *et al.*, *ibid.*, 1976, *10*, 57.

Hydatid cysts. Intrahepatic cysts of *Echinococcus granulosus* were treated with excellent results in 20 patients by freezing the operation area then administering silver nitrate 0.5% to destroy the scolices.— I. Nazarian and F. Saidi, *Z. Tropenmed. Parasit.*, 1971, *22*, 188, per *Trop. Dis. Bull.*, 1971, *68*, 1356.

Ophthalmia neonatorum. In a study of the incidence of ophthalmia neonatorum in 220 000 births, it was found that in 92 365 cases where preparations other than silver nitrate were used the frequency of gonococcal ophthalmia neonatorum was 0.07% whereas where silver nitrate was used the rate was 0.1%. Silver nitrate did not always suppress the development of the condition and seemed no more effective than other agents. While a drop of 1% silver nitrate solution did no harm, there was little evidence that it did any good.— *Lancet*, 1949, *1*, 313.

Of the 49 states of the USA which had made regulations requiring routine prophylactic treatment of the eyes of newborn infants, 22 had specified silver nitrate applications. No evidence had been found to contra-indicate 1% silver nitrate drops when properly packed, handled, and administered. The increasing incidence of gonorrhoea had rendered continued routine prophylaxis necessary.—P.C. Barsam, *New Engl. J. Med.*, 1966, *274*, 731. Fewer local reactions occurred with penicillin than with silver nitrate eye-drops. Penicillin for neonatal prophylaxis should not be abandoned, since it did not appear to sensitise infants.—G. Nathenson (letter), *ibid.*, *275*, 280. Eye-drops containing less than 2% of silver nitrate were considered to be ineffective. Treatment was effective if applied early and prophylaxis was advised only in infants whose mothers were known or suspected to be infected.— E. B. Shaw (letter), *ibid.*, 281. See also P. Kober, *Medsche Klin.*, 1967, *62*, 424.

To prevent gonorrhoeal ophthalmia neonatorum, a 1% solution of silver nitrate was instilled at birth. The chemical conjunctivitis caused by silver nitrate was of short duration.— P. Thygeson, *J. Am. med. Ass.*, 1967, *201*, 902.

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

Pneumothorax. Spontaneous pneumothorax was successfully treated in 132 patients by pleurodesis induced with silver nitrate; repeated pleurodesis was necessary in only 2 patients. It was suggested that this therapy should be used for patients with only small or no blebs visible on thoracoscopy, or with only mild pre-existing lung disease.— I. Anderson and H. Nissen, *Dis. Chest*, 1968, *54*, 230, per *J. Am. med. Ass.*, 1968, *206*, 681.

Wounds. Silver nitrate solution 0.5% was more effective against Gram-positive than Gram-negative bacteria in the treatment of nonthermal war wounds. The solution did not hinder wound healing or epithelialisation of split thickness skin grafts.— J. P. Connors *et al.*, *Archs Surg., Chicago*, 1969, *98*, 119, per *J. Am. med. Ass.*, 1969, *207*, 580.

Preparations

Mitigated Silver Nitrate *(B.P.C. 1968)*. Argenti Nitras Mitigatus; Mitigated Caustic; Argenti Nitras Dilutus. Silver nitrate 1 and potassium nitrate 2, fused together and suitably moulded for application as a caustic to warts and condylomas. Protect from light.

A similar preparation is included in several pharmacopoeias.

Silver Nitrate Stain Remover *(Univ. of Iowa)*. Thiourea $(NH_2CS.NH_2=76{\cdot}12)$ 3 g, citric acid monohydrate 3 g, water to 100 ml. It should be freshly prepared.

Toughened Silver Nitrate *(B.P.)*. Argenti Nitras Induratus; Toughened Caustic; Fused Silver Nitrate; Lunar Caustic; Moulded Silver Nitrate; Stylus Argenti Nitrici. Silver nitrate 95 and potassium nitrate 5, fused together and suitably moulded.

White or greyish-white cylindrical rods or cones, which become grey or greyish-black on exposure to light. Freely soluble in water; sparingly soluble in alcohol. Protect from light.

A similar preparation is included in several pharmacopoeias.

Toughened Silver Nitrate *(U.S.P.)*. Contains not less than 94.5% of $AgNO_3$, the remainder consisting of silver chloride. Store in airtight containers. Protect from light.

Creams

Silver Nitrate Cream. Silver nitrate, 0.5 or 2%, Kalifin-15 20%, water to 100%. The cream was stable with only slight discoloration when stored for 4 weeks in the dark at room temperature; at 0° to 4° there was no discoloration.—*Pharm. Soc. Lab. Rep.* P/68/15, 1968.

Eye-drops

Oculoguttae Argenti Nitratis pro Neonatis *(Dan. Disp.)*. Silver nitrate 670 mg, potassium nitrate 1.2 g, and Water for Injections, 98.13 g.

A similar preparation is included in *F.N.Belg.*

Silver Nitrate Eye-drops *(B.P.C. 1954)*. Gutt. Argent. Nit. Silver nitrate 0.5% w/v, potassium nitrate 1.35% w/v, in Solution for Eye-drops.

Nord. P. has 1% w/w with potassium nitrate 1% w/w in Water for Injections.

Ointments

Unguentum Argenti Nitratis Compositum. Compound Silver Nitrate Ointment. An ointment with this title is included in several pharmacopoeias. It contains silver nitrate 1% and Peru balsam 5 to 10% usually in a basis of yellow soft paraffin or yellow soft paraffin and wool fat.

Ophthalmic Solutions

Silver Nitrate Ophthalmic Solution *(U.S.P.)*. A solution of silver nitrate 0.95 to 1.05% in an aqueous medium. pH 4.5 to 6. It may contain sodium acetate as a buffer. Store in single-dose containers. Protect from light.

Solutions

Ammoniacal Silver Nitrate Solution *(U.S.N.F. XII, 1965)*. Ammoniacal Silver Nitrate, Howe. A solution of diamminosilver nitrate was prepared from silver nitrate 704 g, water 245 ml, and strong ammonia solution to dissolve all but the last trace of precipitate (about 680 ml). It contains 28.5 to 30.5% w/w of Ag and 9 to 9.7% w/w of NH_3. Store in small glass-stoppered containers or in ampoules. Protect from light.

This solution has been employed in dental surgery to deposit silver in exposed dentine or to fill up small crevices in the teeth. After the solution had been applied to the tooth it was followed by a reducing agent such as a 10% formaldehyde solution or eugenol to cause a deposit of metallic silver. The solution has also been employed in the treatment of fungous infections of the nails.

Solutio Argenti Nitratis cum Tetracaino *(Nord. P.)*. Silver nitrate 200 mg, amethocaine nitrate 100 mg, and water 99.7 g.

Proprietary Names

Helvedstensstifter *(Braun, Denm.)*; Lapis *(DAK, Denm.)*; Mova Nitrat Pippette *(Lindopharm, Ger.)*.

5322-m

Silver Protein *(B.P.C. 1968)*. Argentoproteinum; Strong Protein Silver; Strong Protargin; Argentum Proteinicum; Albumosesilber; Protargolum; Proteinato de Plata; Proteinato de Prata.

CAS — 9015-51-4.

Pharmacopoeias. In *Arg.*, *Aust.*, *Belg.*, *Cz.*, *Fr.*, *Hung.*, *Ind.*, *Int.*, *It.*, *Jap.*, *Pol.*, *Port.*, *Roum.*, *Span.*, and *Turk.*

A brown odourless hygroscopic powder containing 7.5 to 8.5% of Ag.

Slowly **soluble** 1 in 2 of water; very slightly soluble in alcohol, chloroform, and ether. A solution in water is neutral to litmus. Solutions may be prepared by shaking the powder over the surface of cold water and allowing it to dissolve slowly, or by triturating the powder to a cream with water and diluting. Solutions are transparent and not coagulated by heat, nor precipitated by the addition of alkali, alkali sulphides, alkali salts, or albumin; they are relatively non-staining. Store in airtight containers. Protect from light.

Adverse Effects. As for Silver (above).

Uses. Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and are used as eye-drops in the treatment of conjunctivitis. Solutions are relatively non-irritant unless they contain more than 10% of silver protein.

Preparations

Silver Protein Eye-drops *(B.P.C. 1963)*. Gutt. [illegible] rot. A solution of silver protein 5%, with [illegible] acetate or nitrate 0.002%, in water. Prepared [illegible] ving, aseptically, the silver protein in a [illegible] solution of phenylmercuric acetate or nitrate [illegible] ferring to the final sterilised container. [illegible] must be freshly prepared. They are adversely [illegible] by alkali. Protect from light.

Proprietary Names

Stillargol *(Mavoly-Spindler, Fr.)*.

5323-b

Mild Silver Protein *(B.P.C. 1968)*. Argento[illegible] Mite; Argentum Vitellinicum; Mild Silver Pro[illegible] Silver Nucleinate; Silver Vitellin; Mild Protar[illegible] nato de Plata; Vitelinato de Prata.

NOTE. The name Mild Silver Protein [illegible] compound because it is less bactericidal and [illegible] than Silver Protein, though it contains more [illegible]

Pharmacopoeias. In *Arg.*, *Belg.*, *Fr.*, *Ind.* [illegible] *Roum.*, *Span.*, *Swiss*, and *Turk.*

A hydroscopic brown powder or nearly black [illegible] granules with a slight odour and taste, contain[illegible] 23% of Ag.

Soluble slowly but completely in water; [illegible] soluble in alcohol, chloroform, and ether. After [illegible] to light it is incompletely soluble in water. [illegible] solution in water is iso-osmotic with serum. In[illegible] with cocaine hydrochloride, but compatible [illegible] atropine sulphate solution. Incompatible with [illegible] acids, alkalis, tannins, and oxidising agents. [illegible] airtight containers. Protect from light.

Preservative for eye-drops. Phenylmercur[illegible] 0.005% was a suitable preservative for [illegible] protein eye-drops sterilised by heating at [illegible] for 30 minutes.— M. Van Ooteghem, *Pharm[illegible] Belg.*, 1968, *45*, 69.

Adverse Effects, Treatment, and Precautions. [illegible] Silver (above).

Argyria. Argyria de[illegible]oped in an elderly [illegible] prolonged use of m[illegible] [illegible]ver protein 10% [illegible] W. A. Parker, *Am. J. Hosp. Pharm.*, 197[illegible]

Uses. Mild silver protein solutions have [illegible] properties similar to those of silver protein [illegible] they contain even lower concentrations of [illegible] and are consequently less irritant to the [illegible] silver protein may be used, therefore, in higher [illegible] trations than silver protein, particularly [illegible] important to avoid irritation of mucous [illegible] Mild silver protein, usually 1 to 5%, is used [illegible] rine as drops or as a spray in nasal infectio[illegible] been applied as a 20% solution in conjunctivit[illegible] the prophylaxis of ophthalmia neonatorum and [illegible] solution to corneal ulcers.

Rhinitis. Mild silver protein (Argyrol) has been [illegible] many years in children with chronic purulent [illegible] and has some value in encouraging nose-blow[illegible] main disadvantage is the irreversible staining [illegible] kerchiefs and pillows.— D. F. N. Harrison, *Prac[illegible] J.*, 1976, *16*, 69.

Preparations

Mild Silver Protein Eye-drops *(B.P.C. 1968)*. [illegible] Argentoprot. Mit. A solution of mild silver protein [illegible] with phenylmercuric acetate or nitrate 0.002% [illegible] Prepared by dissolving, aseptically, the silver [illegible] protein in a sterile 0.002% solution of phenyl[illegible] acetate or nitrate and transferring to the final [illegible] container. The eye-drops must be freshly prepared [illegible] are adversely affected by alkali. Protect from [illegible] *A.P.F.* (Mild Silver Protein Eye-Drops) has [illegible] protein 20% and phenylmercuric nitrate [illegible] Water for Injections.

Silver Protein and Ephedrine Instillation [illegible] Protein and Ephedrine Nasal Drops. Mild [illegible] 5 g, ephedrine 500 mg, phenylmercuric [illegible] freshly boiled and cooled water to 100 ml. [illegible] should be recently prepared. Protect from [illegible]

Proprietary Preparations

Argotone *(Rona, UK)*. Contains mild silver [illegible] and ephedrine hydrochloride 0.9% in [illegible] chloride solution, available as Nasal Drops [illegible] Ready-Spray nasal spray in plastic atomisers [illegible]

Other Proprietary Names

Argincolor *(Fr.)*; Argirol *(Spain)*; Vitargenol [illegible]

ighly with hot 3 per cent hydro-
eight of the precipitate so obtained
n.
er Iodide in tight, light-resistant

TRATE SOLUTION

Ammoniacal Silver Nitrate, Howe

a solution of silver diammino
equivalent of not less than 28.5
and not less than 9.0 Gm. and

. . . . .	704 Gm.
. . . . .	245 ml.
. . . . .	680 ml.
. . . . .	1000 ml.

and dissolve it in the puri-
om temperature and add
e all but the last trace of
his last race of precipitate from

ion is a clear, colorless, almost odorless
ected by light. Its specific gravity is

ate Solution (1 in 10) responds to the
ate, page 683.
Solution add a few drops of formalde-
precipitate is immediately formed (*dis-
monium nitrates*).
Silver Nitrate Solution (1 in 10) add
filter, add 5 ml. of sodium hydroxide
itmus blue.
remains free from even a transient blue

niacal Silver Nitrate Solution add 3 ml.
the clear filtrate tested in a flame on a
of sodium or potassium (*distinction from*

ml. of Ammoniacal Silver Nitrate Solu-
water, 10 ml. of diluted nitric acid, and
rate with 0.1 *N* ammonium thiocyanate.
is equivalent to 10.79 mg. of Ag.
ut 1 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 20 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. Distil 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 3.516 mg. of NH_3.

The ratio between the percentage of ammonia and the percentage of silver closely approximates 1 to 3.16.

Packaging and storage—Preserve Ammoniacal Silver Nitrate Solution in small glass-stoppered, light-resistant containers, or in light-resistant ampuls.

FOR 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, Mild

MILD SILVER PROTEIN

Argentum Proteinicum Mite — Mild Protargin

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 1.6 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.
Please order
Title
Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution.
Source
Archives of Ophthalmology. 101(5):764-5, 1983 May.
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.
Please order
Title
Chemical preparation of skin and eye in ophthalmic surgery: an international survey.
Source
Ophthalmic Surgery. 13(12):1026-9, 1982 Dec.
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.

Rosemary Jacobs
[redacted]

Docket # 98N-0182
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
rm. 1061
Rockville, MD 20852

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[1]. It had been developed and introduced to commerce by Dr. Alfred C. Barnes around 1902[2]. Many silver drugs were fraudulently advertised for decades[3]. Argyrol in particular has been singled out as one of the most fraudulently advertised[4,5]. The ingestion of silver causes argyria, gray skin[6]. 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[7]. Many cases were caused by Argyrol[8] although that never stopped the company from advertising it as "nontoxic"[9].

It is well known that MSP put in the eye caused many cases of argyrosis[10], 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."[11]

There is one case report in the literature that is unusual because just one use of Argyrol drops (1% solution MSP) resulted in argyrosis[12].

In 1928 the Council on Pharmacy and Chemistry refused to readmit Argyrol onto the list of New and Nonofficial Remedies. The principle reason given was the fraudulent adds the company persisted in making. The Council stated that, "Notwithstanding the clinical popularity of Argyrol, its antiseptic efficiency has been seriously questioned. Bacterial culture tests have given variable results, and in the clinical results it has been impossible to distinguish definitely whether improvement is due to the antiseptic or merely to the protective action." Contrary to the manufacturer's claims ophthalmologists did not find that a 25% solution of Argyrol prevented ophthalmia neonatorium although many thought it useful in the treatment of established ophthalmia.[13]

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/

[1] Fung, MC, Bowen, DL Silver Products for Medical Indications: Risk-Benefit Assessment CLINICAL TOXICOLOGY, 34(1), 119-26(1996)
[2] Schack, W. ART AND ARGYROL THE LIFE AND CAREER OF DR. ALBERT C. BARNES Sagamore Press, Inc. NY, 1960 p.51
[3] http://homepages.together.net/~rjstan/
[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
[6] Mack, RB Return with Us Now to Those Thrilling Days of Yesteryear Argyrol and Argyria NCMJ Sept. 1988, Vol 49 #9 p. 451-2
[7] Hill, WR, Pillsbury, DM ARGYRIA THE PHARMACOLOGY OF SILVER The Williams & Wilkins Company 1939 p. 130
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[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] Karcioglu, ZA,. Caldwell, DR Corneal argyrosis: histologic, ultrastructural and microanalytic study CAN J OPHTHALMOL vol. 29 #7 1985 p.257-60
[13] Puckner, WA Council on Pharmacy and Chemistry JAMA March 17, 1928 p.849-51
[14] Isenberg, S, et.. al. Chemical Preparation of the Eye in Ophthalmic Surgery ARCH OPHTHALMOL Vol. 101, May 1983

Monosodium Aspartate: Background for FDA Compounding Advisory Committee

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[1] solution.

Background

Aspartate

Aspartic acid ($HO_2CCH_2CH(NH_2)CO_2H$, 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 of 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.

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

[1] Cardioplegia is defined as an elective procedure for stopping cardiac activity temporarily.

Glutamate/Aspartate		13 mM each
Glucose		> 400 mg%
D5W	Osmolarity	380 to 400 mOsm

*CPD is a citrate-phosphate-dextrose solution, added to make the final Ca^{++} concentration as noted.

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

Floyd D. Loop, MD, Thomas L. Higgins, MD, Ramakanta Panda, MD, Gregory Pearce, MS, and F. George Estafanous, MD. Myocardial protection during cardiac operations. Decreased morbidity and lower cost with blood cardioplegia and coronary sinus perfusion. J. Thorac. Cardiovasc. Surg. 1992;104:608.

Gerald D. Buckberg, M.D., Friedhilm Beyersdorf, M.D, Bradley S. Allen, M.D., and Hon M Robertson, M.D. Integrated Myocardial Management: Background and Initial Application. J. Card. Surg. 1995;10:68.

Rosenkranz, ER, Okamoto F, Buckberg GD, Robertson JM, Ninten-Johansen, J, Bugyi H. Safety of prolonged aortic clamping with blood cardioplegia. III. Aspartate enrichment of glutamate-blood cardioplegia in energy-depleted hearts after ischemic and reperfusion injury. J. Thorac. Cardiovasc. Surg. 1986;91: 428.

Additional References

Eliot R. Rosenkranz, M.D. Substrate enhancement of cardioplegic solution: Experimental studies and clinical evaluation. Ann. Thorac. Surg. 1995; 60: 797.

Gerald D. Bluckberg, MD. Update on current techniques of myocardial protection. Ann. Thorac Surg. 1995; 60:805.

Eliot R. Rosenkranz, M.D., Gerald D. Buckberg, M.D., Hillel Laks, M.D., and Donald G Mulder, M.D. Warm induction of cardioplegia with glutamate-enriched blood in coronary patients with cardiogenic shock who are dependent on inotropic drugs and intra-aortic balloon support. J. Thorac. Cardiovas, Surg. 1983; 86:507.

Eliot R. Rosenkranz, M.D., Fumiyuki Okamoto, M.D., Gerald D. Buckberg, M.D., John M. Robertson, M.D., Jkob Vinten-Johansen, Ph.D., and Helen I. Bugyi, Ph.D. Safety of prolonged aortic clamping with blood cardioplegia. III. Aspartate enrichment of glutamate-blood cardioplegia in energy-depleted hearts after ischemic and reperfusion injury. J. Thorac. Cardiovasc. Surg. 1986: 91:428.

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November 19, 1998

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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. [The Society of Thoracic Surgeons-1995;60:797-800, 1995;60:805-14, 1995;10:68-89, The Journal of Thoracic and Cardiovascular Surgery - Volume 104 Number 3, September 1992]

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

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

Enclosure

98N-0182

C 30

BETAHISTINE DIHYDROCHLORIDE

Table of Contents

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, it's 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]."[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."[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."[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.

Safety

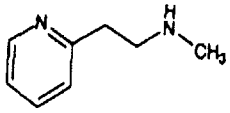
Meanwhile, the safety profile from the literature appears to be benign. There is a single case report of acute bronchospasm. There have been some extrapyramidal reactions. And some rashes are reported. Otherwise the most common AE appears to be GI upset.

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]



.2HCl

CAS #:	5579-84-0
Molecular Formula:	$C_8H_{12}N_2.2HCl$
Molecular Weight:	209.1
Melting Point:	148-149°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. Serc. *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:

Seipel, J. H. and Meyer, J. S. Dementia. *J Clin.,J Pharm.* 1975;15: 144 & 1974; 14: 280.

Tighilet, B., Leonard, J. and Lacour, M. Betahistine dihydrochloride treatment facilitates vestibular compensation in the cat. *Journal of Vestibular Research,* 1995; 5(1): 53-66.

Oostervald, W. J. Betahistine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study. *Journal of Laryngology & Otology.* 1984; 98(1): 37-41.

Petermann, W. and Mulch, G. Long-term therapy of Meniere's disease. Comparison of the effects of betahistine dihydrochloride and hydrochlorothiazide. *Fortschritte der Medizin*, 1982; 100(10): 431-435.

Fraysse, B., Bebear, J. P., and Dubreiul, C. Betahistine dihydrochloride versus flunarizine. A double-blind study on recurrent vertigo with or without cochlear syndrome typical of Meniere's disease. *Acta Oto-Laryngologica*, 1991: 490 (Suppl): 1-10.

Pfaltz, C. R. and Aoyagi, M. Calcium-entry blocker in the treatment of vestibular disorders. *Acta Oto-Laryngologica*, 1988; 460 (Suppl): 135-142.

Oosterveld, W. J. Efect of betahistine dihydrochloride on induced vestibular nystagmus: a double blind study. *Clinical Otolaryngology*, 1987; 12(2): 131-135.

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

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.

[1] Diener HC, Foh M, et al. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study Group. Cephalalgia. 1996; 16(6):441-7.

Another report[2] suggests that higher doses of cyclandelate (1600mg/day) may be more effective.

Other published studies report similar findings.

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.

Conclusions for Migraine

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

CYCLANDELATE AND DIABETIC RETINOPATHY

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

Diabetic retinopathy[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.[4]

---

[2] Gerber WD, Schellenberg R, et al. Cyclandelate versus propranolol in the prophylaxis of migraine--a double-blind placebo-controlled study. Funct.Neurol. 1995; 10(1):27-35.
[3] *Cecil Textbook of Medicine, 19th edition*, (1992), pages 1307-1308.
[4] DCCT Study Group. 1995. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of diabetic retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44(8):968-983.

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).

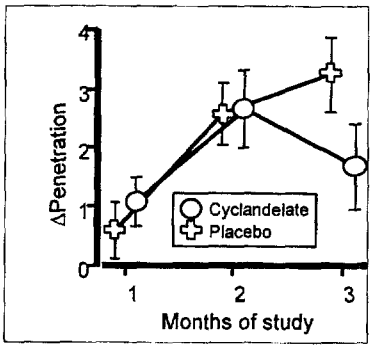


Figure 1. Change in fluorescein penetration (Cunha-Vaz et al.).

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).

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[5] Cunha-Vaz JG, Reis Fonseca J, and Hagenouw JRB. 1977. Treatment of early diabetic retinopathy with cyclandelate. *Br. J. Ophthalmology* 61:399-404.

[6] Mota MC, Leite E, Ruas MA, Verjans HL, Blakemore CB, and Cunha-Vaz JG. 1987. Effect of cyclospasmol on early diabetic retinopathy. Internat *Ophthalmology* 10:3-9.

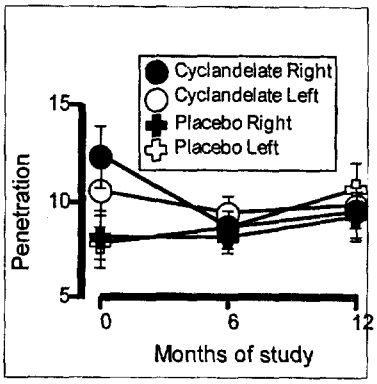

Figure 2. Fluorescein penetration (Mota et al.).

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

1. Mastrosimone F, et al. Efficacy and tolerance of cyclandelate versus pizotifen in the prophylaxis of migraine. J Med 1992; 23(1):1-16.

2. Nappi G, et al. Comparative efficacy of cyclandelate versus flunarizine in the prophylactic treatment of migraine. Drugs 1987;33(Suppl 2):103-9.

3. Siniatchkin M, et al. Clinical efficacy and central mechanisms of cyclandelate in migraine: a double-blind placebo-controlled study. Funct.Neurol. 1998; 13(1):47-56.

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, acetonitrile, ethyl acetate and dimethylformamide (USP classification). Cyclandelate can decompose by hydrolysis to mandelic acid and 3,3,5-trimethylcyclohexanol. However, when cycloandelate 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 –titrimetry, 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, Spasmocyclon, Spasmocyclone
Cyclospansmol
Benzenenacetic Acid, Clandilon, Cyclandelate, Cyclolyt, 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:

Cook, P. and James, I. Cerebrovascular Disease. *New Engl. J. Med.* 1981;305:1508 and 1560.

Young, J. Studies on the role of Cyclandelate in Cerebrovascular disease. *Br. J. Psychiat*, 1974; 124:177.

Hall, P. *J. Am. Geriat. Soc.* 1976; *24:41.*

Davies, G. *Age and Ageing.* 1977; 6:156.

Rao, D. B. *J. Am. Geriat. Soc.* 1977; 25:548.

Brasseur, R. *Angiology.* 1978; 29: 121.

Capote, B. and Parikh. *J. Am. Geriat. Soc.*, 1978; 26:360.

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

Cunha-Vaz, J. G. Diabetic Retinopathy. *Br. J. Ophthal.* 1977; 61:399.

Coffman, J. D. Peripheral vascular disease. *New Engl. J. Med.* 1979;300:713.

Hester, T. O., Theilman, G., and Green, W. Cyclandelate in the management of tinnitus: a randomized, placebo-controlled study. *Otolaryngol Head Neck Surg*, 1998; 118(3Pt1): 329-332.

Sauer, S., Schellenberg, R., and Hofmann, H. C. Functional imaging - first steps in an objective quantitative classification of migraine. *Eur J Med Res*, 1997: 29(9): 368-376.

Aparasu, R. R. and Fliginger, S. E. Inappropriate medication prescribing for the elderly by office-based physicians. *Ann Pharmacother*, 1997;31(7-8):823-829.

Schellenberg, R., Todorova, A., and Wedekind, W. Pathophysiology and psychopharmacology of dementia--a new study design. 2. Cyclandelate treatment--a placebo-controlled double-blind clinical trial. *Neuropsychobiology*, 1997; 35(3):132-142.

Diener, H. C. Migraine--diagnosis, differential diagnosis and therapy. *Ther Umsch*, 1997;54(2):64-70.

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 popranolol. The Study Group. In summary, cyclandelate has a comparable efficacy to that of popranolol. Both drugs were better than placebo. Both active treatments were well tolerated. *Cephalalgia*, 1996; 16(6):441-447.

Gerber, W. D., Schellenberg, R., and Thom, M. Cyclandelate versus popranolol in the prophylaxis of migraine–a double-blind placebo-controlled study. *Funct Neurol*, 1995; 10(1):27-35.

Mota, M. C., Leite, E., and Ruan, M.A. Effect of cyclospasmol on early diabetic retinopathy. *Int Opthalmol*, 1987; 10(1):3-9.

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:

supplement to the fourth edition. Comments received too late for consideration for the first supplement will be considered for later supplements.)

ADDRESSES: Submit written comments and supporting data and documentation to the NAS/IOM Committee on Food Chemicals Codex, National Academy of Sciences, 2101 Constitution Ave. NW., Washington, DC 20418. Copies of the new monographs and proposed 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, 12420 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.edu/codex.

FOR FURTHER INFORMATION CONTACT:

Fatima N. Johnson, Committee on Food Chemicals Codex, Food and Nutrition Board, National Academy of Sciences, 2101 Constitution Ave. NW., Washington, DC 20418, 202–334–2580; or

Paul M. Kuznesof, Center for Food Safety and Applied Nutrition (HFS–247), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3009.

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 28413), 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 (1–800–624–6242; 202–334–3313; FAX 202–334–2451; Internet http://www.nap.edu) 2101 Constitution Ave. NW., Lockbox 285, Washington, DC 20055.

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.edu/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 Dicarbonate
Glyceryl Palmitostearate
4-Hexylresorcinol
Sodium Lignosulfonate
Sucrose Fatty Acid Esters
Sugar Beet Fiber
Reduced Lactose Whey
Reduced Minerals Whey
Whey Protein Concentrate
Autolyzed 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)
Carbon Dioxide (combine nitric oxide and nitrogen dioxide limits, and revise test)
Dextrin (add sulfur dioxide test)
Dioctyl Sodium Sulfosuccinate (revise identification test)
Enzyme-Modified Fats (modify enzyme-modified milkfat monograph)
L-Glutamic Acid (revise identification test B)
Konjac Flour (revise identification test B)
Magnesium Phosphate, Dibasic (decrease loss on ignition limits)
Niacin (revise identification tests)
Niacinamide (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 comments 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. 96–30727 Filed 12–2–96; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 94N–0168] DES 78

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

AGENCY: Food and Drug Administration, HHS.

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 Initial 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.

EFFECTIVE DATE: January 2, 1997.

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, 12420 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, 5600 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

Cyclospasmol® is a drug consisting of 200 milligrams (mg) of cyclandelate. (G–33.2 at 7.)[1] 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 these pre-1962 drugs for effectiveness is 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, 617 (1973), citing 21 U.S.C. 355(e)(3).)

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 30443), 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 June 25, 1979, AHP filed a request for a hearing, and this request was granted by the Commissioner on October 18, 1984 (49 FR 40972). Under

[1] The Dockets Management Branch used the letter "G" to refer to the Government exhibits by the participants.

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 adequate and well-controlled clinical trials, and concluded that the approval 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, including: (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 requiring 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 concluding section of the ALJ's decision, which is appropriately entitled "Conclusions," to argue that the ALJ simply announced his findings in one sentence decrees. (AHP Exceptions at 9, citing the ALJ's Initial Decision (I.D.) at 23.)

An identical 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). *Gilbertville Trucking Co.* v. *United States*, 196 F. Supp. 351 (D. Mass. 1961); *State Corporation Comm.* v. *United States*, 184 F. Supp. 691 (D. Kan. 1959). "An agency which issues opinions in narrative and expository form may continue to do so without making separate findings of fact and conclusions of law." Attorney General's Memorandum on the Administrative Procedure Act 86 (1947). So too may an Administrative Law Judge.

(Commissioner's Decision on Lutrexin, 41 FR 14406 at 14410, April 5, 1976.)

I have reviewed the ALJ's decision in the present matter, and I find that it comports with the previously cited requirements of the Administrative Procedure Act and FDA regulations. As in the Commissioner's decision regarding Lutrexin, I find that the ALJ fully set out the reasons for his decision in the narrative explanation section of the Initial Decision. Therefore, I find no merit in AHP's argument.

AHP further argues that the ALJ erred in concluding that at least two adequate and well-controlled studies are necessary to establish efficacy. (AHP Exceptions at 2 n.1; I.D. at 8.) As with AHP's previous objection, this issue, too, has been settled in previous Commissioner's decisions. In 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. 75N-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 Deprol (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 ruling 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 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 Mysteclin. 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." (Commissioner's Decision on Mysteclin, 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, "if enough pair-wise comparisons are made, some comparisons will be 'statistically significant' by chance alone." (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, 46.)

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.

h. *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 January 2, 1997.

Dated: November 12, 1996.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 96-30648 Filed 12-2-96; 8:45 am]

BILLING CODE 4160-01-P

[Docket No. 96D-0334]

Procedures for Issuance of and Review and Response to Materials Submitted in Response to Clinical Hold 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" (OD-R-8-96, 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:

CBER Information: For additional copies of the documents submit written requests to the Manufacturers Assistance and Communication Staff (HFM-42), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist that office in processing your requests. The document may also be obtained by mail or FAX by calling the CBER FAX Information System at 1-888-CBER FAX, or 301-827-3844. Persons with access to the Internet may obtain the document using FTP, the World Wide Web (WWW), or bounce-back e-mail. For FTP access, connect to CBER at "ftp://ftp.fda.gov/CBER/". For WWW access, connect to CBER at "http://www.fda.gov/cber/cberftp.html". For bounce-back e-mail send a message to "INDHOLD@a1.cber.fda.gov".

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-ON-DEMAND System at 1-800-342-2722, or 1-301-827-0577. An electronic version of the documents is also available via Internet using FTP, Gopher, or the World Wide Web (WWW). For FTP, connect to the CDER anonymous FTP server at cdvs2.cder.fda.gov and change to the "guidance" directory. For Gopher, connect to the CDER Gopher server at

CYCLANDELATE

LD50 is greater than 2 g/kg.

It has produced ataxia, altered sleep, flushing, headache, tachycardia.

CYCLANDELATE (Cyclospasmol ®)

1-Physicians Desk Reference, 40th Ed., pg. 1947.

2-Diener, H.C., et al., Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. Cephalalgia, 1996, 16: 441-447.

REFERENCES

1. Hester TO, Theilman G, Green W, et al. Cyclandelate in the management of tinnitus: a randomized, placebo-controlled study. Otolaryngol Head Neck Surg 1998; 118(3 Pt 1):329-32.

2. Sauer S, Schellenberg R, Hofmann HC, et al. Functional imaging of headache- first steps in an objective quantitative classification of migraine. Eur J, Med Res 1997; 2(9):367-76.

3. Aparasu RR, Fliginger SE. Inappropriate medication prescribing for the elderly by office-based physicians. Ann Pharmacother 1997; 31(7-8):823-9.

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5. Diener HC. [Migraine-diagnosis, differential diagnosis and therapy]. Ther Umsch 1997; 54(2):64-70.

6. Diener HC, Foh M, Iaccarino C, et al. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. Cephalalgia 1996; 16(6):441-7.

7. Gerber WD, Schellenberg R, Thom M, et al. Cyclandelate versus propranolol in the prophylaxis of migraine—a double-blind placebo-controlled study. Funct Neurol 1995; 10(1):27-35.

8. Mota MC, Leite E, Ruas MA, et al. Effect of cyclospasmol on early diabetic retinopathy. Int Ophthalmol 1987; 10(1):3-9.

9. Cunha-Vaz JG, Reis Fonseca J, Hagenouw JRB. Treatment of early retinopathy with cyclandelate. British Journal of Ophthalmology 1977; 61:399-404.

HYRDAZINE SULFATE
Table of Contents

FDA Review/Recommendation

Background Information

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 3/22/99

From: Saul Malozowski
Acting Medical Team Leader

Subject: Hydrazine AC meeting

To: Solomon Sobel
Division Director, DMEDP 4/9/99

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 patents 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. Oyer, M.D.
Hydrazine sulfate

July 20, 1994

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 Trostle

Stephen Trostle
CSO-DMEDP

cc: IND Arch
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HFD-510/~~STrostle~~ \HS.MEM
RHeller