

# SECURITIES AND EXCHANGE COMMISSION

## FORM DEFA14A

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#### ICN PHARMACEUTICALS INC /DE/

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(Name of Registrant as Specified in its Charter)

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December 19, 1993

Dear Shareholder/Investor:

Enclosed for your information are new materials that exemplify the solid science behind the company's antiviral Virazole (ribavirin) and its research and development programs:

- 1) Four investigational studies of ribavirin capsules in the treatment of hepatitis C from the October, 1993 issue of the medical journal HEPATOLOGY. It includes an abstract from the National Institutes of Health Liver Unit that preliminarily reports that in 16 patients receiving ribavirin ". . . prolonged ribavirin therapy was associated with significant improvement in serum ALT levels (despite unchanged serum HCV RNA levels) and in hepatic lobular necrosis" (Vol. 18, No. 4, Pt. 2, 1993). Serum ALT levels and the degree of hepatic lobular necrosis are key parameters for monitoring chronic hepatitis C. Ribavirin is not yet approved for the indication of hepatitis C by the FDA.
- 2) An article entitled "antiviral therapy of hepatitis C - present and future" from the JOURNAL OF HEPATOLOGY (1993: 17, Suppl. 3).
- 3) New treatment guidelines from the American Academy of Pediatrics on the use of aerosolized Virazole to treat severe lower respiratory tract infections caused by respiratory syncytial virus (RSV). They are authored by the Academy's Committee on Infectious Diseases, which includes liaison representatives from NIH, CDC and FDA. The Academy recommends Virazole as the standard of care in all high-risk RSV babies, including those with a number of underlying medical conditions. The new guideline is based on the safe and efficacious use of aerosolized Virazole in more than 100,000 babies since it was introduced in the U.S. in 1986.

Sincerely,

Jack Sholl  
Senior Vice President  
Public Relations

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HEPATOLOGY

THE  
AMERICAN ASSOCIATION  
FOR THE  
STUDY OF LIVER DISEASES

POSTGRADUATE COURSE  
& 44TH ANNUAL MEETING  
NOVEMBER 4-7, 1993

CHICAGO MARRIOTT HOTEL  
CHICAGO, ILLINOIS

OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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HEPATOLOGY Vol. 18, No. 4, Pt. 2, 1993

145 RANDOMIZED, DOUBLE BLIND PLACEBO-CONTROLLED TRIAL OF RIBAVIRIN THERAPY  
FOR CHRONIC HEPATITIS C.

AM Di Bisceglie, MW Fried, MG Swain, NV Bergasa, C Yurdaydin, LH  
Simpson, R Sallie, H Conjeevaram, D Kleiner, Y Park, JH Hoofnagle. Liver

58 pts with chronic hepatitis C entered a randomized, double-blind controlled trial of ribavirin (600mg BID orally for 12 mos) vs placebo. All had HCV RNA in serum (by PCR) with elevated serum ALT values (>2X ULN) for >6 mos and chronic hepatitis on liver biopsy. To date, 32 pts have completed therapy, 16 on ribavirin and 16 placebo. The 2 groups were well matched with regard to age, gender, duration and source of hepatitis, liver histology, serum ALT and HCV RNA levels. During therapy with ribavirin, ALT values became and remained normal in 4 pts (25%, responders). ALTs fell by more than 50% in 7 pts (44%, partial responders); overall mean values decreased by 47% (p<.01) by the end of therapy (Table). No pt lost serum HCV RNA and mean levels of HCV RNA did not change (branched DNA assay, Chiron). After stopping therapy, ALT values rose in most pts, including 2 of 4 responders. The histologic activity index (HAI) decreased with ribavirin, hepatic lobular necrosis improving most (mean 3.3 vs 2.3, p<.05).

<TABLE>

<CAPTION>

Time	ALT	AST	HCT	WBC	HAI	HCV RNA (ag/ml)
<S>	<C>	<C>	<C>	<C>	<C>	<C>
Pre	186	130	44.7	6.6	12.5	2273
Post	88*	69	38.9*	5.5*	11.4	1947

</TABLE>

(\*p<.01) Only 1 placebo-treated pt had a partial response, none lost HCV RNA and liver histology appeared to worsen (mean HAI 11.1 vs 12.3, p=ns). Ribavirin was associated with hemolysis requiring dose reduction in 2 pts and a mild decrease in lymphocyte counts (2401 vs 1506/mm<sup>3</sup>, p<.01). The dose was reduced in 2 pts for non-specific constitutional symptoms. Thus, prolonged ribavirin therapy was associated with significant improvement in serum ALT levels (despite unchanged serum HCV RNA levels) and in hepatic lobular necrosis.

146 COMBINATION THERAPY OF  $\alpha$ -INTERFERON AND RIBAVIRIN IN PATIENTS WITH CHRONIC HEPATITIS C: AN INTERIM REPORT.

MY Lai, PM Yang, JH Kao, JT Wang, HS Lee, and DS Chen. Grad. Inst. Clin. Med., Dept. Int. Med., and Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan.

For chronic hepatitis C, treatment with  $\alpha$ -interferon alone can induce long-term normalization of serum ALT activities in only about 15-25% of the patients after cessation of the drug. Ribavirin is a nucleoside analog which has significant antiviral activity against HCV. To improve the efficacy of treatment for chronic hepatitis C, we designed a combination therapy with  $\alpha$ -interferon and ribavirin. Sixty patients with positive anti-HCV, persistently elevated serum ALT for more than 6 mo with levels at least twice the upper limit of the normal range before therapy, chronic hepatitis without cirrhosis of liver histology, were recruited. There were 34 males and 26 females, with mean age of 51 yr (range: 31 to 69 yr). They were randomized into 3 groups: (1) Group A received interferon- $\alpha$ -2a (Roferon-A) (3 million units thrice weekly) and ribavirin (1200 mg/day) for 6 mo; (2) Group B received interferon- $\alpha$ -2a 3 million units thrice weekly alone for 6 mo; (3) Group C were controls. Up to now, 9 patients in either group A or B have completed the treatment. In group A, normalization of serum ALT activities was rapidly achieved in all patients. By the end of therapy (6 mo), 7 (78%) had normal ALT activity and the result have sustained up to 5 mo after cessation of the therapy. In contrast, in group B, only 3 (33%) patients had normalization of serum ALT activities at the end of therapy, and all suffered from relapse of elevated serum ALT one mo after cessation of the drug. In group C, all patients had persistent abnormal serum ALT levels. Only mild and tolerable side effects were encountered in the treated patients. We conclude that combination therapy of  $\alpha$ -interferon and ribavirin for chronic hepatitis C can remarkably increase the response rate during therapy. The long-term effect of this novel regimen seems promising but awaits further observation.

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375 COMBINATION THERAPY WITH RIBAVIRIN AND  $\alpha$ -INTERFERON IN PATIENTS WITH CHRONIC HEPATITIS C RESISTANT TO  $\alpha$ -INTERFERON TREATMENT.

S. Brillanti, C. Masci, M. Miglioli and L. Barbara, Dept. of Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy.

The aim of this pilot study was to evaluate the role of combination therapy with ribavirin and  $\alpha$ -interferon (IFN) in patients with chronic hepatitis C who failed to respond to IFN therapy (NR) or who had a relapse from response to IFN therapy (RR). Ten consecutive NR patients and 10 consecutive RR patients entered into the study. In each patient, IFN therapy had been stopped at least 12 months before entry. All patients were positive for anti-HCV (ELISA-2 and RIBA-2), serum HCV-RNA (PCR) and had chronic active hepatitis on liver biopsy. They were randomly assigned to receive other combination of ribavirin, 800 mg a day, with IFN, 3 MU tiw, for 6 mo., (10 patients), or IFN alone. 3 MU tiw, for 6 mo., (10 patients). The two groups were comparable concerning age (43.3+/-6.1 vs. 48.3+/-4.4 yr.), sex (6 vs. 5 males), pre-therapy ALT levels (110.1+/-28.6 vs. 151.3+/-32.6 U/L), and liver histology (5 vs. 4 cirrhosis). All

patients were prospectively observed for at least 12 mo. Results are summarized in the table:

<TABLE>

<CAPTION>

	IFN + Ribavirin (n=10) <C>	IFN alone (n=10) <C>	p <C>
<S> Normal ALT			
Initial	0	0	NS
Final	7	4	NS
6 mo. later	5	0	<0.02

</TABLE>

In the combination therapy group: (a) The sustained normalization of ALT levels occurred in 3/5 (60%) RR patients and in 2/5 (40%) NR patients: (b) The sustained normalization of ALT levels was always accompanied by sustained loss of serum HCV-RNA. Mild hemolytic anemia was observed in some patients treated with combination therapy. In conclusion, combination therapy with ribavirin and IFN seems able to induce a sustained biochemical and virological response in patients with chronic hepatitis C resistant to a-interferon treatment.

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1144 TREATMENT OF HEPATITIS C VIRAL INFECTION (HCV) IN THE TRANSPLANTED PATIENT WITH RIBAVARIN.

M. Rezieg, I. Altraif, C. Roach, P. Greig, E. Cole, M. Kraiden, G. Levy. Multi-Organ Transplant Unit, Univ. of Toronto, Canada.

It has been suggested that post-transplant HCV infection can lead to serious, rapidly progressive and ultimately fatal liver disease. Immunosuppression has been reported to accelerate the severity and course of this infection as compared to HCV infection in non-immunosuppressed patients. Ribavarin is a nucleoside analogue with a broad spectrum of anti-viral activity for both RNA and DNA viruses. We investigated the efficacy of Ribavarin in 6 patients who have developed chronic hepatitis C infection post-transplant. Patient characteristics are described in the table below.

<TABLE>

<CAPTION>

PT.#	AGE	SEX	TX.	SERUM HCV		AST (IU/L)		BILIRUBIN (umol/L)	
				PCR RNA	EIA II	PRE	POST	PRE	POST

<S>	<C>	<C>	<C>	<C>	<C>	<C>	<C>	<C>	<C>
1	59	M	Liver/ Kidney	+	+	115	27	145	24
2	58	M	Kidney	+	+	73	24	38	20
3	28	M	Kidney	+	+	107	66	14	17
4	56	M	Liver	+	+	131	32	34	13
5	23	M	Kidney	+	+	74	24	16	8
6	18	M	Liver	+	+	846	72	180	22

</TABLE>

TX = transplant

All patients were male with a mean age of 45.3 +/- 15.9 years. Patients were treated with Ribavirin (1 gram per day in 2 divided doses for 3 months). Liver biopsies at initiation of therapy showed moderate to severe chronic active hepatitis and fibrosis. Liver biochemistry and hematology were followed weekly and patients assessed monthly. All patients developed mild to moderate hemolysis, and in one patient the medication had to be stopped. The mean AST and bilirubin prior to treatment were 224 +/- 305 IU/L and 76.1 +/- 68.4 umol/L respectively. At discontinuation, the AST and bilirubin decreased to 40.8 +/- 22 IU/L and 17.3 +/- 5.9 umol/L respectively. Patients clinically felt better and to date there have been no biochemical relapses. In conclusion a 3 month course of Ribavirin appears to be efficacious for chronic HCV infection in the setting of organ transplantation although longer follow up and larger trials must be performed in order to firmly conclude this.

Consent of publication has not been received from the American Association for the Study of Liver Diseases as of the date of this filing.

AMERICAN ACADEMY OF PEDIATRICS

USE OF RIBAVIRIN IN THE TREATMENT OF RESPIRATORY SYNCYTIAL VIRUS INFECTION

RE9329

Committee on Infectious Diseases

Ribavirin is an antiviral drug that was approved by the Food and Drug Administration in 1986 for aerosol treatment of serious respiratory syncytial virus (RSV) infections in hospitalized children. Ribavirin has a broad spectrum of antiviral activity in vitro, where it inhibits replication of RSV, influenza, parainfluenza, adenovirus, measles, Lassa fever, and Hantaan viruses. Proof of efficacy for human infection has been obtained in double-blind placebo-controlled studies of RSV, (1,2) Lassa fever, and Korean hemorrhagic fever. Presently, only anecdotal reports support the efficacy of

this drug for treatment of measles or parainfluenza. Ribavirin treatment for RSV infections has been controversial because of the aerosol route of administration, concern for potential toxicity for exposed persons, cost, and the unpredictable and highly variable course of illness in the absence of specific therapy. These issues necessitate ongoing review of ribavirin therapy and the following updated recommendations by the American Academy of Pediatrics.

## BACKGROUND

### RSV DISEASE

Respiratory syncytial virus is the most important cause of lower respiratory tract disease in infants and young children. Disease usually appears in yearly outbreaks in the winter or spring, and essentially all children become infected during their first 3 years of life. The number of infected infants who require hospitalization has been estimated to range from 1 to 50 per 1000 in different locations. Currently, the mortality rate in hospitalized infants who previously were healthy is low (less than 1%). In infants with underlying diseases, however, the mortality can be much higher. Conditions that increase the risk of severe or fatal RSV infection are cyanotic or complicated congenital heart disease (including pulmonary hypertension); underlying pulmonary disease, especially bronchopulmonary dysplasia; prematurity; and immunodeficiency disease or therapy causing immunosuppression at any age.

Most previously healthy infants infected with RSV do not require hospitalization, and many who are hospitalized improve within a few days with supportive care and are discharged after a stay ranging from 3 to 5 days. Long-term sequelae of RSV infec-

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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tion are difficult to assess. Evidence recently has accumulated suggesting that some infected children develop long-term abnormalities in pulmonary function.<sup>(3)</sup> Although these abnormalities may be subclinical in most children, some subjects have recurrent wheezing. Whether treatment of the initial respiratory syncytial virus infection can alter the rate or severity of such sequelae is unknown.

Aerosolized ribavirin is the first specific drug available for treatment of RSV infections. It is a synthetic nucleoside analogue (1-B-d-ribofuranosyl-1,2,4-triazole-3-carboxamide) resembling guanosine and inosine; it appears to interfere with the expression of messenger RNA and to inhibit viral protein synthesis. It is not significantly incorporated into host cell RNA or DNA.

#### CLINICAL STUDIES

Ribavirin is administered as aerosolized particles small enough (median aerosol diameter, 1 to 2  $\mu$ m) to reach the lower respiratory tract. It is delivered via an oxygen hood, tent, or mask for 12 to 20 hours each day for a mean of 4 days. In controlled studies involving both healthy infants and those with underlying disease, clinical improvement was greater in ribavirin recipients than in placebo recipients. Ribavirin had a beneficial effect on some signs, such as retraction and rales, but not on others, such as fever and wheezing. However, these latter signs were present in only a minority of patients. Improvement in arterial blood oxygenation following ribavirin therapy has been substantial. In one study, the treated group had a mean arterial oxygen pressure (Pao<sub>2</sub>) of 49.4 mm Hg at the start of therapy and 62.4 mm Hg at the end, a mean increase of 13 mm Hg, which was significantly greater than the comparable values for the placebo group (at the start and end of therapy 52 mm Hg and 56 mm Hg, respectively). (4) The effect of therapy on persistence of virus in secretions differed in various studies.

No appreciable toxicity has been observed in any of the controlled trials or in other follow-up studies. Although reversible bronchospasm has been observed occasionally (less than 0.1%), hyperactivity of the airways has not been demonstrated in studies of pulmonary function during administration of ribavirin aerosol. (4-6) The effect of ribavirin aerosol on pulmonary function was examined in adult volunteers infected with RSV in a controlled, double-blind study. Serial pulmonary function tests, which included carbachol challenge, showed no alterations in volunteers during ribavirin therapy or when tested]

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month later. The long-term effects of ribavirin on pulmonary function and on the sequelae of RSV infection require further investigation.

In mechanically ventilated infants, most of whom were previously healthy, ribavirin treatment was safe and was associated with a reduced need for mechanical ventilation and supplemental oxygen, shorter duration of hospitalization, and cost-effectiveness. (7)

One potential problem is deposition of the drug in the ventilator delivery system, which appears to be dependent on temperature, humidity, and electrostatic forces. This deposition can lead to malfunction or obstruction of

the expiratory valve, resulting in inadvertently high positive end-expiratory pressures. The use of one-way valves in the inspiratory lines, a breathing circuit filter in the expiratory line, and frequent monitoring and filter replacement by trained staff have been effective in preventing these problems.

Experience with antiviral agents used to treat other viruses has raised the additional concern of development of resistance to ribavirin by RSV. To date, no change in susceptibility of any viral isolate to ribavirin has been observed, even with prolonged administration.

#### SAFETY FOR HEALTH CARE PERSONNEL

Although mucous membrane irritation has been reported following exposure to ribavirin (especially in the eyes of contact lens wearers), it occurs in a small percentage of exposed personnel and is reversible.(8) Reproductive and teratogenic toxicities were observed in pregnant rodents administered oral ribavirin. These effects were not reproduced in baboons and have not been reported in humans. Studies have indicated that although absorption of ribavirin can occur in health care personnel from environmental exposure, no deleterious effects have been reported. Concern about the safety of ribavirin has led some hospitals to apply strict precautions for use of ribavirin to minimize exposure of health care workers.

A review of animal and human data on ribavirin safety is summarized and interpreted as follows:(9)

1. In hamsters after a single oral dose of 2.5 mg/kg, and in rats after a daily oral dose of 10 mg/kg for 60 days or longer, fetal malformations have been noted. In rabbits, the species most sensitive to the effects of ribavirin, skeletal malformations were observed after daily oral administration of 0.1 to 0.3 mg/kg for 12 days. In contrast, seven pregnant baboons were treated orally with 60 to 120 mg/kg of ribavirin for 4 consecutive days, during the time of fetal organogenesis. The offspring of six of seven of these baboons showed no evidence of teratogenicity. The seventh animal aborted at day 45 (60-mg dose) but no traces of implantation were recovered, implying fetal death and resorption prior to organogenesis and prior to ribavirin therapy.(9) (10)
2. Extrapolation from these animal experiments involving oral administration of ribavirin to circumstances of human exposure to ribavirin aerosol is difficult, especially in view of species differences in teratogenicity and the high doses administered.

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3. During treatment with aerosolized ribavirin, dissemination of the drug

in the environment of the patient can occur, with the potential for inhalation by those caring for treated children. However, while 60% to 70% of the inhaled drug may be deposited in the airways, absorption from the respiratory tract into the circulation is minimal. In infants receiving aerosolized ribavirin, the mean peak plasma concentration was less than 1 umol/L at a time when the peak concentrations in endotracheal secretions were greater than 1700 umol/L.(11)

Studies of health care personnel also have demonstrated minimal absorption. In one study of 19 non-pregnant nurses who were caring for infants receiving ribavirin by aerosol treatment via an oxygen tent, hood, or ventilator, nurses were exposed for a mean of 8 hours per day during a 3-day period (a total of 20 to 35 hours).(12) Total air exchanges occurred 5.4 to 24 times per hour in the patients' rooms. Blood samples for analysis of ribavirin were obtained 1 day before exposure, 1 hour after the final exposure, and 3 to 5 days later; urine was collected before and 3 to 5 days after exposure. Ribavirin was not detected in any sample of plasma, erythrocytes, or urine. The lower limit of sensitivity of the radioimmunoassay used to measure ribavirin in the study was 0.02 ug/mL. In a similar study of health care personnel caring for infants treated with ribavirin, 90 samples of serum, urine, and erythrocytes were assayed for ribavirin.(13) Ribavirin was detected in a concentration of 0.44 ug/mL in only one erythrocyte sample. (The minimum level of detection of the test used was 0.02 ug/mL.) The concurrent serum and urine samples were negative. No symptoms were reported by any health care workers in this study.

These findings and the lack of validated reports of adverse effects in human fetuses after 7 years of clinical use of the drug in the United States suggest that the teratogenic risk of ribavirin exposure in humans is extremely low. The National Institute for Occupational Safety and Health (NIOSH) recently conducted a study at a Florida Hospital, where the technique they employed consistently found small concentrations of ribavirin in the postshift urine of nurses. No clinical findings were reported in association with these observations.(14) NIOSH recommends review of work policies and institution of engineering controls in order to reduce environmental concentration of ribavirin in the patient's room.

## RECOMMENDATIONS

Experience in more than 100,000 patients indicates that aerosolized ribavirin treatment for RSV infection is both safe and effective. As with other antiviral therapy, the maximum benefit will be derived by early treatment of high-risk patients. The route of administration, cost, and need for hospitalization support a strategy of selective use of ribavirin as follows:

1. Patients at High Risk for Complications Due to Other Conditions.  
Ribavirin treatment is recom-

mended for the following patients hospitalized with RSV lower respiratory tract disease:

- a. Infants at high risk for severe or complicated RSV infection, including those with complicated congenital heart disease (including pulmonary hypertension); those with bronchopulmonary dysplasia, cystic fibrosis, and other chronic lung conditions; premature infants; children with immunodeficiency (especially those with acquired immunodeficiency syndrome or severe combined immunodeficiency disease); recent transplant recipients; and patients undergoing chemotherapy for malignancy.
  - b. Infants who are severely ill. Because severity of illness is often difficult to judge clinically in infants with RSV infection, determination of blood gas concentrations is often necessary. Values for PaO<sub>2</sub> of less than 65 mm Hg (ie, oximetry reading less than 90%) and increasing concentration of carbon dioxide arterial pressure (PaCO<sub>2</sub>) are useful indicators of severity.
  - c. All patients mechanically ventilated for RSV infection.
2. Treatment for Hospitalized Infants. Ribavirin treatment should also be considered for hospitalized infants who may be at increased risk of progressing from a mild to a more complicated course by virtue of young age (less than 6 weeks) or underlying condition, such as multiple congenital anomalies or certain neurologic or metabolic diseases (eg, severe cerebral palsy, myasthenia).
3. Diagnosis of RSV Infection. Rapid diagnostic techniques to identify RSV antigen in respiratory secretions should be performed when the child is admitted to the hospital. Tissue culture isolation requires 3 to 5 days. If rapid tests are not available, patients in the recommended categories who have bronchiolitis or pneumonia clinically compatible with RSV infection and who are admitted during the RSV season (generally November to April) should be considered for ribavirin therapy. If the etiology of the infant's pulmonary disease is subsequently found to be an agent other than RSV, ribavirin therapy can be discontinued. If no agent is identified initially as the cause of the lower respiratory tract disease, but the most likely clinically diagnosis remains RSV infection and the infant is severely ill, continuation of treatment is reasonable. Further diagnostic efforts to ascertain the causative agent should be undertaken, recognizing that false-negative rapid diagnostic test results have been noted in 5% to 20% of cases.
4. Administration. Ribavirin is nebulized by a small-particle aerosol generator into an oxygen hood, tent, or mask from a solution containing 20 mg of ribavirin per milliliter of water. The generator is supplied with the drug by the manufacturer. The aerosol is administered for 12 to 20 hours per day, usually for 3 to 5 days depending on the patient's clinical course; a longer duration of therapy may be useful in immunodeficient patients. A recent study noted good patient tolerance and favorable ribavirin pharmacokinetics when a regimen of 60

mg/mL for 2 hours three times daily was used; however, the efficacy of this dosage has not been proven.(11) Maximal therapeutic responses usually are not noted after 2 to 4 days of treatment.

5. Isolation of Patients. Treatment with ribavirin does not eliminate the need for contact isolation of patients with RSV.(15)
6. Precautions for Health Care Personnel and Visitors. Health care personnel and visitors should be informed about the potential but unknown risks of environmental exposure to ribavirin. In-service education for hospital personnel is most effective just prior to the RSV season. While evidence of human teratogenicity is lacking, in view of the embryopathic effects in nonprimate animals, pregnant women should be advised not to care directly for patients who are receiving ribavirin.(16) Several methods have been employed to lower environmental exposure. For example, aerosol administration should be stopped temporarily when the hood or tent is open. Also, the drug should be administered in well-ventilated rooms (at least six air changes per hour).

No additional precautions to protect patients, visitors, or hospital workers in the room are required. Masks designed to block absorption of 1- to 2-ug particulate droplets may reduce inhalation of ribavirin, but clinical studies are lacking. Standard surgical masks do not block particles of this size. Gloves and gowns are not essential since dermal absorption of ribavirin appears to be negligible. However, gloves and gowns may lower the risk of nosocomial spread of RSV. Scavenger devices to lower the escape of aerosolized ribavirin into a room also can be used.(17) Additional research and clinical experience are needed to establish more specific guidelines regarding occupational exposure.

Committee on Infectious Diseases, 1992 to 1993

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#### 504 RIBAVIRIN FOR RESPIRATORY SYNCYTIAL VIRUS

Consent of publication has not been received from the American Academy of Pediatrics as of the date of this filing.

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Antiviral therapy of hepatitis C - present and future

The current recommendations for therapy of chronic hepatitis C are a 6-month course of alpha-interferon in doses of 3 million units 3 times weekly. Patients should have compensated chronic liver disease with elevations in serum aminotransferases, serologic evidence of hepatitis C virus (HCV) infection and chronic hepatitis by liver biopsy. At present, a long-term beneficial response to alpha-interferon occurs in only 10-25% of patients. The modest long-term response rate and the restricted recommendations for use of interferon leave several unresolved issues regarding therapy of this disease. Do patients with atypical, severe or advanced disease warrant therapy? What is the optimal dose and duration of treatment? How can one increase the response rate to interferon? How can one predict which patients are likely to benefit from therapy? Which patients are likely to relapse if therapy is stopped? Ultimately, what is needed to answer these issues are better techniques to assess HCV infection and monitor therapy as well as more effective and better-tolerated agents that can be used alone or in combination with alpha-interferon.

Key words: Chronic hepatitis; Cirrhosis; Hepatitis C virus; Controlled trials; Antiviral therapy; Inteferon; Ribavirin; Polymerase chain reaction

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Pilot studies (1) followed by multiple randomized controlled trials (2-10) have documented that alpha-interferon is effective in suppressing disease activity and inducing remissions in disease in a high proportion of patients with chronic hepatitis C. Treatment with doses of 3-5 million units (MU) of alpha-interferon subcutaneously thrice weekly has been associated with a serum biochemical response in 40-70% of patients and a long-term, sustained improvement in aminotransierases in 10-25% of patients. In several trials, this improvement in serum biochemical tests has been shown to correlate well with improvements in liver histology and function 13-61. More recently, retrospective analyses have shown that improvements in clinical features of disease are associated with a decrease or loss of serum hepatitis C virus (HCV) RNA from the serum and liver (11). These studies have provided the basis for the licensing and approval of alpha-interferon as therapy for chronic hepatitis C in most countries of the world.

These initial controlled trials provided the basis for current recommendations for the use of alpha-interferon as therapy of chronic hepatitis C. Treatment is recommended for patients with compensated chronic hepati-

normal and liver biopsy demonstrates chronic hepatitis disease activity. Interferon should be given at a dose of 3 MU subcutaneously thrice weekly for 6 months. If improvements in aminotransferases has not occurred after 2-3 months of treatment, therapy can be discontinued early. The dose of interferon can be increased to 5 MU thrice weekly if a partial response occurs. However, side effects of interferon are common, and are often dose-limiting. Indeed, a sizeable proportion of patients receiving 3 MU of interferon will require a decrease in dose because of intractable fatigue, anxiety, depression, leukopenia or other side effects. This approach to treatment should lead to improvements in approximately 50% of patients and sustained responses in 10-25%.

#### UNRESOLVED ISSUES

Although alpha-interferon is now considered standard therapy for chronic hepatitis C, there are several unresolved issues concerning its use. Some major issues are

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#### ANTIVIRAL THERAPY OF HEPATITIS C

TABLE 1

Therapy in chronic hepatitis C: unresolved issues

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How to treat patients with atypical or severe disease?  
What is the optimal dose and duration of therapy?  
What are the predictors of a response to therapy?  
What are the predictors of a relapse after therapy?  
How can one increase the response rate?  
-----

TABLE 2

Alpha-interferon therapy in chronic hepatitis C: atypical patients

-----  
Decompensated cirrhosis  
Children  
Atypical serology ianti-HCV-negative:  
Immunocompromised patients  
Organ transplant patients  
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(Table 1): (1) How and whether to treat patients with atypical or complicated disease? (2) What is the optimal dose and duration of alpha-interferon therapy?

(3) How can one predict which patients are likely to have a beneficial response to therapy? (4) How can one identify whether a relapse is likely to occur when therapy is stopped? (5) How can one increase the response rate?

## ATYPICAL PATIENTS

Alpha-interferon is recommended largely for patients with well-compensated chronic hepatitis C who have serologic evidence of disease anti-HCV or HCV-RNA, elevations in serum aminotransferase activities, chronic hepatitis by liver biopsy, and no other serious complicating illness. Not included in these recommendations are patients with clinically apparent cirrhosis, children, patients with atypical serologic patterns and patients who are immunocompromised either because of an immune deficiency or immunosuppressive therapy (Table 2).

Patients with decompensated cirrhosis due to hepatitis C represent an important group that warrants some form of therapy short of liver transplantation. There have been no prospective randomized studies of alpha-interferon in patients with advanced cirrhosis due to chronic hepatitis C, but anecdotal reports indicate that a proportion of such patients responds to treatment with improvements in aminotransferases and liver histology (12). However, the response rate to alpha-interferon is somewhat lower in patients with cirrhosis (5) and the improvements induced by therapy are difficult to sustain. A prospective, controlled trial of alpha-interferon in patients with early or mildly decompensated liver disease (Child's Class A or B) is needed.

Chronic hepatitis C is rare in childhood. As a result

there have been no controlled trials of alpha-interferon treatment in children. There is no reason to believe that children will respond differently to interferon from adults. Indeed, children tolerate interferon very well. Consequently, interferon therapy is indicated in children with chronic hepatitis C.

Therapy of patients with suspected chronic hepatitis C and atypical serologic markers can be problematic. At least 80% of patients with chronic hepatitis C will have anti-HCV in serum using a first-generation assay and the remainder will have HCV-RNA in serum (11,13,14). A higher percentage will be reactive using a second-generation anti-HCV test (15). Unfortunately, second-generation anti-HCV tests and assays for HCV-RNA are not commercially available in all areas of the world.

At present, most patients are diagnosed as having chronic hepatitis C based

upon the finding of anti-HCV in serum by a first-generation ELISA along with elevations in serum aminotransferases and liver histology compatible with chronic hepatitis. However, this approach is not without shortcomings. Some patients with chronic hepatitis C will be non-reactive for anti-HCV (false negatives) (11,13). In addition, some patients with other forms of liver disease (autoimmune hepatitis or alcoholic liver disease) will test positive for anti-HCV by ELISA due to a non-specific reaction (false positives) (16,17). The history of an exposure to blood or blood products (transfusion, drug addiction, medical care exposure) is helpful in verifying the diagnosis of hepatitis C, but these features are not always present in the clinical history and are not always reliable. These difficulties become important because there is evidence that auto-immune chronic active hepatitis will worsen with alpha-interferon therapy (18). For this reason, additional efforts should be made to exclude patients with autoimmune features of disease before using alpha-interferon, particularly if HCV-RNA testing is not available and if there is no history of exposure, or if clinical features of the disease are atypical. Autoimmune hepatitis should be considered in young patients, particularly women, if the disease is severe or there is no exposure history. In any case, alpha-interferon should be withdrawn rapidly if there is worsening of serum aminotransferases with alpha-interferon therapy (18,19). Severe worsening of disease and even fatalities due to exacerbation of the underlying hepatitis have been reported during alpha-interferon therapy of hepatitis C.

Another group of problematic patients are those who are immunocompromised, such as patients who have human immunodeficiency virus (HIV) infection, who have renal failure, who have received an organ transplant, or who are receiving immunosuppressive

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therapy. There are no reports available concerning treatment of such patients. Anecdotal results suggest that, in contrast to immunocompromised patients with chronic hepatitis B, those with chronic hepatitis C may benefit from alpha-interferon therapy (12). The role of interferon therapy in this group deserves further evaluation, particularly in view of new information suggesting that chronic hepatitis C can be severe following organ transplantation (20,21).

A final group of patients in whom studies of therapy are needed are those with acute hepatitis C. Preliminary, small trials of alpha- and beta-interferon in acute hepatitis C have indicated that early treatment may prevent chronicity (22-24). In most of these studies, interferon was given for 6-12 weeks and patients were followed for the development of chronic hepatitis C for up to 1 year after treatment. In all 3 studies reported to date, the interferon-treated patients have demonstrated a more rapid decrease of aminotransferase levels into the normal range and a lower rate of chronicity at 6 months and 1 year. Overall, however, the decrease in chronicity with interferon treatment has been limited. Obviously, larger controlled trials with longer periods of

follow-up evaluation are needed. At present alpha-interferon should not be used in acute hepatitis C outside of a controlled trial.

#### DOSE AND DURATION OF THERAPY

The currently recommended regimen of alpha-interferon for chronic hepatitis C is 3 MU subcutaneously thrice weekly for 6 months. However, this dose may not be high enough for some patients, and a 6-month course may be suboptimal in reliably inducing a sustained response. Several ongoing trials are comparing regimens of 3, 5 and 10 MU and courses of 6 and 12 months. In a randomized, placebo-controlled trial conducted at the National Institutes of Health, patients received either alpha-interferon (2 MU) or placebo thrice weekly for 6 months (4). Afterwards patients who received placebo were crossed over to receive interferon for up to 12 months in doses of 2-5 MU thrice weekly depending upon response in aminotransferase levels and tolerance. While the overall response rate was similar with both regimens, the sustained response rate was higher with the 12-month course of treatment (Fig.1).

Thus, at present, the optimal dose and duration of therapy are unclear. There also may be variation between patients in response to different doses. Until prospective, randomized controlled trials demonstrate a benefit for higher doses of alpha-interferon or for longer courses of therapy, one must recommend a dose of 3 MU and a

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[GRAPH]

Di Bisceglie et al 1990

Fig. 1. Overall response rate among 41 patients with chronic hepatitis C who were entered into a randomized, controlled trial of alpha-interferon and who were given interferon (2 MU) (n = 21) or placebo (n = 20) thrice weekly for 6 months. Eighteen of the placebo recipients were then crossed over to receive interferon (2-3 MU) thrice weekly for 12 months. The upper bars show the overall response rate, the lower bars the sustained response rate associated with each treatment.

6-month course of treatment. The dose should be increased only if the response is partial.

#### PREDICTORS OF RESPONSE

Only 50% of patients with chronic hepatitis C respond to alpha-interferon therapy. It would be very helpful if there were clinical or serologic features that would predict which patients were likely to respond to therapy and which were not. Unfortunately, retrospective analyses from the controlled trials of interferon have failed to identify any clinical, serum biochemical, serological

or histological feature of disease that reliably predicted a response to treatment (3-6.25). Importantly, the presence or titers of anti-HCV or HCV-RNA in serum did not identify patients who were likely to have a response to interferon (11). These findings were in contrast to hepatitis B, where the height of serum aminotransferases and level of HBV-DNA are helpful in identifying patients who are likely to benefit from treatment (26). In some studies, patients who lacked anti-HCV and who had cirrhosis histologically were less likely to benefit from therapy (5). However, these correlations have been weak and cannot be used to decide on whether to use interferon or not.

## ANTIVIRAL THERAPY OF HEPATITIS C

## PREDICTORS OF RELAPSE

The optimal duration of therapy is not currently known. Different patients may require different lengths of treatment. What is needed is a means of monitoring treatment that would correctly identify when HCV has been cleared and a sustained clinical response could be expected. In this way, the duration of therapy would be based upon attainment of a complete response. This is the case in chronic hepatitis B. in which serological markers can identify when a sustained response is attained: the loss of HBV-DNA and HBeAg from serum indicates clearance of HBV replication 1261.

Several clinical, serum biochemical, serological and histological features have been analyzed as possible means of monitoring therapy in chronic hepatitis C. (Table 3). Obviously, serum aminotransferase levels and liver histology, while correlating with a response to therapy, do not predict a sustained response. More recently, specific serologic markers have been analyzed for a possible role in monitoring treatment and identifying when a complete and lasting response in chronic hepatitis C. has occurred.

Most patients with chronic hepatitis C. have anti-HCV in serum in titers ranging from 10 degrees to 10(5). Retrospective analyses have shown that titers of anti-HCV as assessed by first-generation ELISA did not change in a consistent manner during alpha-interferon therapy (11.27). A preliminary report has suggested that IgM anti-HCV, which is frequently detectable in patients with chronic hepatitis C. decreases and often disappears during treatment in patients who have a sustained response but not in those without a response or with a transient response ???. If these findings are confirmed, IgM anti-HCV testing might play an important role in monitoring patients and deciding how long to continue treatment.

The technique of polymerase chain reaction (PCR) is a very sensitive means of detecting specific nucleic acid sequences and has been used to detect and quantify HCV-RNA in serum (11.13.14). Most patients with chronic hepatitis C. have HCV-RNA in serum in titers ranging from 10 degrees to 10(5). Testing of stored serum from

TABLE 3

Alpha-interferon therapy in chronic hepatitis C. potential means for monitoring

therapy.

-----  
Serum aminotransferase levels  
Liver histology  
Antibody to HCV  
IgM antibody to HCV  
HCV-RNA in serum  
HCV-RNA in liver  
HCV antigens in liver  
-----

patients treated with alpha-interferon has shown that levels of this viral marker decrease on treatment and HCV-RNA becomes undetectable in most patients with a beneficial response to treatment (Fig. 2). Levels decrease only slightly or not at all in patients with no or only a partial response. However, HCV-RNA reappears in patients with a relapse after therapy is stopped and loss of HCV-RNA, while correlating well with a

[HCV-RNA CHART]

Responders                      Non-responders                      Placebo

Fig. 2. Serum levels of HCV-RNA in 39 patients who entered a randomized placebo controlled trial of alpha-interferon in chronic hepatitis C. HCV-RNA fell to undetectable levels in most patients who responded to treatment but in only rare patients without a response and in no patients who received placebo.

### [Serum ALT CHART]

Fig. 3. Course of a patient with chronic hepatitis C treated with alpha-interferon. Serum ALT levels fell into the normal range and serum HCV-RNA became undetectable and remained undetectable even when therapy was stopped.

### [INTERFERON NORMS CHART]

Fig. 4. Course of a patient with chronic hepatitis C treated with alpha-interferon. Serum ALT levels fell into the normal range and serum HCV-RNA became undetectable. However, a relapse of disease and reappearance of serum HCV-RNA occurred when treatment was stopped.

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response to alpha-interferon treatment, does not predict a sustained response (Figs. 3 and 4). Nevertheless, these findings provide a virologic basis for assessing the efficacy of alpha-interferon in chronic hepatitis C. The major effect of interferon appears to be inhibition of viral replication, and thus long-term responses occur when there has been sustained clearance of virus.

Obviously, better markers are needed to assess and monitor therapy and to provide guidance in when to initiate and when to stop therapy. Further assessments of serum antibody responses and evaluation of HCV-RNA and HCV antigens in liver tissue (28) may yet provide the serologic tools to place therapy of hepatitis C on a more rational basis.

### HOW TO INCREASE THE RESPONSE RATE

While alpha-interferon has provided the first effective treatment for chronic hepatitis C, this treatment is effective in only 50% of patients and a long-term response occurs in only 10-25% of patients. Furthermore, interferon is difficult to administer, is quite expensive, and has multiple side effects which can be dose-limiting. Better tolerated and more effective therapies are needed. Use of repeated courses of alpha-interferon in patients with partial or temporary responses has been only partially beneficial.

Characterization of the genome of HCV suggests that it is a flavivirus-like virus. A tissue culture or simple animal model of hepatitis C would be extremely helpful in further characterizing this virus and to screen for antiviral agents of potential use. Until there is such an in vitro or in vivo method for monitoring HCV replication, however, antiviral studies will have to be done in human patients with this disease. For this reason, the majority of agents that have been used in chronic hepatitis C are those that have been previously evaluated for other conditions in man (Table 4). The agent that

currently demonstrates the most promise is ribavirin.

Ribavirin (1-β-D-ribofuranosyl 1,2,4-triazole-3-carboxamide) is a guanosine analogue that has been evaluated extensively as therapy of respiratory syncytial virus and HIV infection in man (29). Ribavirin is especially attractive as it is absorbed orally and is well tolerated, its only significant side effect being a dose-related hemolysis that is generally mild, subclinical, and rapidly reversible when therapy is stopped. Ribavirin was initially tried in chronic hepatitis C based upon its safe clinical profile and its known activity against many RNA viruses including some flaviviruses.

Wetland and co-workers from Sweden treated 10

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TABLE 4

Therapy of chronic hepatitis C; potential agents

-----  
Antivirals

Ribavirin, acyclovir, adenine arabinoside,  
foscarnet, dideoxynucleosides, azathymidine,  
ganciclovir, suramin

Biologic response modifiers

Alpha-, beta- and gamma-interferon, interleukins  
2, 4 and 6, colony-stimulating factors, tumor  
necrosis factor

Immunomodulators

Prednisone, thymosin, levamisole  
-----

patients with chronic hepatitis C with ribavirin for 12 weeks in doses of 1000-1200 mg per day (30). Serum aminotransferases decreased by 60% during therapy but rose to pre-treatment values soon after ribavirin was stopped. Changes in liver histology and levels of HCV-RNA or anti-HCV were not reported.

At the National Institutes of Health, we have completed a pilot study of oral ribavirin therapy in 13 patients with chronic hepatitis C (31). Ribavirin was administered in gradually escalating doses for 6 months. Serum aminotransferases levels fell in all 13 patients and became normal in 4 (28%). The average decrease in aminotransferases was 67%. However, even after 6 months of treatment, liver biopsies demonstrated no consistent improvement in degree of inflammation or hepatocellular necrosis. When ribavirin was stopped, serum aminotransferases rose to pre-treatment levels in most, but not all patients.

On the other hand, ribavirin was well-tolerated even at the highest doses (1200 mg.d) and the only side effect noted was a mild, clinically silent, hemolytic anemia.

Interesting differences were noted between the clinical and serologic responses in patients treated with ribavirin versus those treated with alpha-interferon. The serum aminotransferases fell much more slowly with ribavirin than with interferon therapy. However, the ultimate level of improvement in aminotransferases was the same with both drugs: with both there was a 60-70% decrease from pre-treatment levels (3.31). Another difference was that aminotransferase levels decreased in all patients treated with ribavirin but in only 50-70% of those treated with interferon. This fact underscores the peculiar variability in response to alpha-interferon therapy. Finally, serum levels of HCV-RNA decreased markedly in all patients who responded to alpha-interferon therapy (11); in contrast, HCV-RNA levels decreased only slightly during ribavirin therapy (31).

The encouraging preliminary observations on the effects of ribavirin therapy in chronic hepatitis C have

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#### ANTIVIRAL THERAPY OF HEPATITIS C

led to a prospective, randomized, double-blind controlled trial of ribavirin (1200 mg/d) versus placebo for 12 months that is being carried out at the National Institutes of Health (Fig. 5). This trial began in November 1991 and will include 50-60 patients entered over a 6-month period. Meanwhile, more studies are needed on the potential combination of ribavirin with alpha-interferon as well as dose-finding studies based upon response of aminotransferases to ribavirin therapy.

#### THE FUTURE OF THERAPY OF HEPATITIS C

Future research into therapy for hepatitis C will focus on more agents than alpha-interferon and ribavirin (Table 4) and on a broader spectrum of this disease. It is possible that multiple antiviral agents with activity against HCV will be identified. Indeed, initial results suggest that this virus is quite sensitive to inhibition and that lowering the level of virus leads to amelioration of disease. In addition to a search for more agents to treat this disease, further studies of alpha-interferon and riba-

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[GRAPH]

Fig. 5. Design of randomized controlled trial of ribavirin in chronic hepatitis C.

virin therapy are needed. Particularly important are studies in patients with clinically apparent cirrhosis, in children, in patients with unusual forms of the disease and immunocompromised patients.

Thus, the future of antiviral therapy in chronic hepatitis C will help to fill in the gaps in knowledge about the correct use of alpha-interferon but will also focus on newer antiviral agents that alone or in combination with interferon promise to provide a relatively safe but highly effective therapy for all patients with liver disease due to hepatitis C.

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VIRAZOLE (R)  
(ribavirin for inhalation solution)

PRESCRIBING INFORMATION

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WARNINGS:

USE OF AEROSOLIZED VIRAZOLE IN PATIENTS REQUIRING MECHANICAL VENTILATOR ASSISTANCE SHOULD BE UNDERTAKEN ONLY BY PHYSICIANS AND SUPPORT STAFF FAMILIAR WITH THE SPECIFIC VENTILATOR BEING USED AND THIS MODE OF ADMINISTRATION OF THE DRUG. STRICT ATTENTION MUST BE PAID TO PROCEDURES THAT HAVE BEEN SHOWN TO MINIMIZE THE ACCUMULATION OF DRUG PRECIPITATE, WHICH CAN RESULT IN MECHANICAL VENTILATOR DYSFUNCTION AND ASSOCIATED INCREASED PULMONARY PRESSURES (SEE WARNINGS).

SUDDEN DETERIORATION OF RESPIRATORY FUNCTION HAS BEEN ASSOCIATED WITH INITIATION OF AEROSOLIZED VIRAZOLE USE IN INFANTS. RESPIRATORY FUNCTION SHOULD BE CAREFULLY MONITORED DURING TREATMENT. IF INITIATION OF AEROSOLIZED VIRAZOLE TREATMENT APPEARS TO PRODUCE SUDDEN DETERIORATION OF RESPIRATORY FUNCTION, TREATMENT SHOULD BE STOPPED AND REINSTITUTED ONLY WITH EXTREME CAUTION, CONTINUOUS MONITORING AND CONSIDERATION OF CONCOMITANT ADMINISTRATION OF BRONCHODILATORS (SEE WARNINGS).

VIRAZOLE IS NOT INDICATED FOR USE IN ADULTS. PHYSICIANS AND PATIENTS SHOULD BE AWARE THAT RIBAVIRIN HAS BEEN SHOWN TO PRODUCE TESTICULAR LESIONS IN RODENTS AND TO BE TERATOGENIC IN ALL ANIMAL SPECIES IN WHICH ADEQUATE STUDIES HAVE BEEN CONDUCTED (RODENTS AND RABBITS); (SEE CONTRAINDICATIONS).

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DESCRIPTION

VIRAZOLE (R) is a brand name for ribavirin, a synthetic nucleoside with antiviral activity. VIRAZOLE for inhalation solution is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 900 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg of ribavirin per ml, pH approximately 5.5. Aerosolization is to be carried out in a Small Particle Aerosol Generator (SPAG-2) nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1H-1, 2, 4-triazole-3-carboxamide, with

the following structural formula:

[FORMULA] Ribavirin is a stable, white crystalline compound with a maximum solubility in water of 142 mg/ml at 25 degrees C and with only a slight solubility in ethanol. The empirical formula is C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> and the molecular weight is 244.21.

#### CLINICAL PHARMACOLOGY

#### MECHANISM OF ACTION

In cell cultures the inhibitory activity of ribavirin for respiratory syncytial virus (RSV) is selective. The mechanism of action is unknown. Reversal of the in vitro antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

#### MICROBIOLOGY

Ribavirin has demonstrated antiviral activity against RSV in vitro(1) and in experimentally infected cotton rats.(2) Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16 ug/ml; however, results may vary with the test system. The development of resistance has not been evaluated in vitro or in clinical trials.

In addition to the above, ribavirin has been shown to have in vitro activity against influenza A and B viruses and herpes simplex virus, but the clinical significance of these data is unknown.

#### IMMUNOLOGIC EFFECTS

Neutralizing antibody responses to RSV were decreased in aerosolized VIRAZOLE treated infants compared to placebo treated infants.(3) One study also showed that RSV-specific IgE antibody in bronchial secretions was decreased in patients treated with aerosolized VIRAZOLE. In rats, ribavirin administration resulted in lymphoid atrophy of the thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies. The clinical significance of these observations is unknown.

#### PHARMACOKINETICS

Assay for VIRAZOLE in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

VIRAZOLE brand of ribavirin, when administered by aerosol, is absorbed systemically. Four pediatric patients inhaling VIRAZOLE aerosol

administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 uM, with a mean concentration of 0.76 uM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling aerosolized VIRAZOLE administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 uM, with a mean concentration of 6.8 uM.

The bioavailability of aerosolized VIRAZOLE is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations of ribavirin are 85% to 98% less than the concentration that reduced RSV plaque formation in tissue culture. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and it is unknown whether plasma concentrations or respiratory secretion concentrations of the drug better reflect intracellular concentrations in the respiratory tract.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days (the half-life of erythrocytes). The extent of accumulation of ribavirin following inhalation therapy is not well defined.

#### ANIMAL TOXICOLOGY

Ribavirin, when administered orally or as an aerosol, produced cardiac lesions in mice, rats, and monkeys, when given at doses of 30, 36 and 120 mg/kg or greater for 4 weeks or more (estimated human equivalent doses of 4.8, 12.3 and 111.4 mg/kg for a 5 kg child, or 2.5, 5.1 and 40 mg/kg for a 60 kg adult, based on body surface area adjustment). Aerosolized ribavirin administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen in the lungs following exposure at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

#### INDICATIONS AND USAGE

VIRAZOLE is indicated for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus. Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Only severe RSV lower respiratory tract infection should be treated with VIRAZOLE. The vast majority of infants and children with RSV infection have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of VIRAZOLE aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with VIRAZOLE should be based on the severity of the RSV infection. The presence of an underlying condition such as prematurity, immunosuppression or cardiopulmonary disease may increase the

severity of clinical manifestations and complications of RSV infection.

Use of aerosolized VIRAZOLE in patients requiring mechanical ventilator assistance should be undertaken only by physicians and support staff familiar with this mode of administration and the specific ventilator being used (see Warnings, and Dosage and Administration).

## DIAGNOSIS

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence(3,4) or ELISA(5) before or during the first 24 hours of treatment. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection. Non-culture antigen detection techniques may have false positive or false negative results. Assessment of the clinical situation, the time of year and other parameters may warrant reevaluation of the laboratory diagnosis.

## DESCRIPTION OF STUDIES

**NON-MECHANICALLY-VENTILATED INFANTS:** In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, aerosolized VIRAZOLE treatment had a therapeutic effect, as judged by the reduction in severity of clinical manifestations of disease by treatment day 3.(3,4) Treatment was most effective when instituted within the first 3 days of clinical illness. Virus titers in respiratory secretions were also significantly reduced with VIRAZOLE in one of these original studies.(4) Additional controlled studies conducted since these initial trials of aerosolized VIRAZOLE in the treatment of RSV infection have supported these data.

**MECHANICALLY-VENTILATED INFANTS:** A randomized, double-blind placebo controlled evaluation of aerosolized VIRAZOLE at the recommended dose was conducted in 28 infants requiring mechanical ventilation for respiratory failure caused by documented RSV infection.(6) Mean age was 1.4 months (SD, 1.7 months). Seven patients had underlying diseases predisposing them to severe infection and 21 were previously normal. Aerosolized VIRAZOLE treatment significantly decreased the duration of mechanical ventilation required (4.9 vs 9.9 days, p=0.01). Intensive patient management and monitoring techniques were employed in this study. These included endotracheal tube suctioning every 1 to 2 hours; recording of proximal airway pressure, ventilatory rate, and F(1)O(2) every hour; and arterial blood gas monitoring every 2 to 6 hours. To reduce the risk of VIRAZOLE precipitation and ventilator malfunction, heated wire tubing, two bacterial filters connected in series in the expiratory limb of the ventilator (with filter changes every 4 hours), and water column pressure release valves to monitor internal ventilator pressures were used in connecting ventilator circuits to the SPAG-2.

Employing these techniques, no technical difficulties with VIRAZOLE administration were encountered during the study. Adverse events consisted of bacterial pneumonia in one case, staphylococcus bacteremia in one case and two cases of post-extubation stridor. None were felt to be related to VIRAZOLE

administration.

## CONTRAINDICATIONS

VIRAZOLE is contraindicated in individuals who have shown hypersensitivity to the drug or its components, and in women who are or may become pregnant.

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during exposure to the drug, Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted (rodents and rabbits). Therefore, although clinical studies have not been performed, it should be assumed that VIRAZOLE may cause fetal harm in humans. Studies in which the drug has been administered systemically demonstrate that ribavirin is concentrated in the red blood cells and persists for the life of the erythrocyte.

## WARNINGS

SUDDEN DETERIORATION OF RESPIRATORY FUNCTION HAS BEEN ASSOCIATED WITH INITIATION OF AEROSOLIZED VIRAZOLE USE IN INFANTS. Respiratory function should be carefully monitored during treatment. If initiation of aerosolized VIRAZOLE treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and reinstated only with extreme caution, continuous monitoring, and consideration of concomitant administration of bronchodilators.

## USE WITH MECHANICAL VENTILATORS

USE OF AEROSOLIZED VIRAZOLE IN PATIENTS REQUIRING MECHANICAL VENTILATOR ASSISTANCE SHOULD BE UNDERTAKEN ONLY BY PHYSICIANS AND SUPPORT STAFF FAMILIAR WITH THIS MODE OF ADMINISTRATION AND THE SPECIFIC VENTILATOR BEING USED. Strict attention must be paid to procedures that have been shown to minimize the accumulation of drug precipitate, which can result in mechanical ventilator dysfunction and associated increased pulmonary pressures. These procedures include the use of bacteria filters in series in the expiratory limb of the ventilator circuit with frequent changes (every 4 hours), water column pressure release valves to indicate elevated ventilator pressures, frequent monitoring of these devices and verification that ribavirin crystals have not accumulated within the ventilator circuitry, and frequent suctioning and monitoring of the patient (see Clinical Studies).

Those administering aerosolized VIRAZOLE in conjunction with mechanical ventilator use should be thoroughly familiar with detailed descriptions of these procedures as outlined in the SPAG-2 manual.

## PRECAUTIONS

### GENERAL

Patients with severe lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status (see SPAG-2 manual).

### DRUG INTERACTIONS

Clinical studies of interactions of VIRAZOLE with other drugs commonly used to treat infants with RSV infections, such as digoxin, bronchodilators, other antiviral agents, antibiotics or anti-metabolites, have not been conducted. Interference by VIRAZOLE with laboratory tests has not been evaluated.

### CARCINOGENESIS AND MUTAGENESIS

Ribavirin increased the incidence of cell transformations and mutations in mouse Balb/c 3T3 (fibroblasts) and L5178Y (lymphoma) cells at concentrations of 0.015 and 0.03-5 mg/ml, respectively (without metabolic activation. Modest increases in mutation rates (3-4x) were observed at concentrations between 3.75-10.0 mg/ml in L5178Y cells in vitro with the addition of a metabolic activation fraction. In the mouse micronucleus assay, ribavirin was clastogenic at intravenous doses of 20-200 mg/kg, (estimated human equivalent of 1.67-16.7 mg/kg, based on body surface area adjustment for a 60 kg adult). Ribavirin was not mutagenic in a dominant lethal assay in rats at intraperitoneal doses between 50-200 mg/kg when administered for 5 days (estimated human equivalent of 7.14-28.6 mg/kg, based on body surface area adjustment; see Pharmacokinetics).

In vivo carcinogenicity studies with ribavirin are incomplete. However, results of a chronic feeding study with ribavirin in rats, at doses of 16-100 mg/kg/day (estimated human equivalent of 2.3-14.3 mg/kg/day, based on body surface area adjustment for the adult), suggest that ribavirin may induce benign mammary, pancreatic, pituitary and adrenal tumors. Preliminary results of 2 oral gavage oncogenicity studies in the mouse and rat (18-24 months; doses of 20-75 and 10-40 mg/kg/day, respectively (estimated human equivalent of 1.67-6.25 and 1.43-5.71 mg/kg/day, respectively, based on body surface area adjustment for the adult)) are inconclusive as to the carcinogenic potential of ribavirin (see Pharmacokinetics). However, these studies have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages in mice) and retinal degeneration (in rats).

### IMPAIRMENT OF FERTILITY

The fertility of ribavirin-treated animals (male or female) has not been fully investigated. However, in the mouse, administration of ribavirin at doses

between 35-150 mg/kg/day (estimated human equivalent of 2.92-12.5 mg/kg/day, based on body surface area adjustment for the adult) resulted in significant seminiferous tubule atrophy, decreased sperm concentrations, and increased numbers of sperm with abnormal morphology. Partial recovery of sperm production was apparent 3-6 months following dose cessation. In several additional toxicology studies, ribavirin has been shown to cause testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (estimated human equivalent of 2.29 mg/kg/day, based on body surface area adjustment; see Pharmacokinetics). Lower doses were not tested. The reproductive capacity of treated male animals has not been studied.

PREGNANCY: CATEGORY X

Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted. Teratogenic effects were evident after single oral doses of 2.5 mg/kg or greater in the hamster, and after daily oral doses of 0.3 and 1.0 mg/kg in the rabbit and rat, respectively (estimated human equivalent doses of 0.2 and 0.14 mg/kg based on body surface area adjustment for the

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adult). Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. Ribavirin caused embryoletality in the rabbit at daily oral dose levels as low as 1 mg/kg. No teratogenic effects were evident in the rabbit and rat administered daily doses of 0.1 and 0.3 mg/kg, respectively with estimated human equivalent doses of 0.01 and 0.04 mg/kg, based on body surface area adjustment (see Pharmacokinetics). These doses are considered to define the "No Observable Teratogenic Effects Level" (NOTEL) for ribavirin in the rabbit and rat.

Following oral administration of ribavirin in the pregnant rat (1.0 mg/kg) and rabbit (0.3 mg/kg), mean plasma levels of drug ranged from 0.10-0.20 uM [0.024-0.049 ug/ml] at 1 hour after dosing, to undetectable levels at 24 hours. At 1 hour following the administration of 0.3 or 0.1 mg/kg in the rat and rabbit (NOTEL), respectively, mean plasma levels of drug in both species were near or below the limit of detection (0.05 uM; see Pharmacokinetics).

Although clinical studies have not been performed, VIRAZOLE may cause fetal harm in humans. As noted previously, ribavirin is concentrated in red blood cells and persists for the life of the cell. Thus the terminal half-life for the systemic elimination of ribavirin is essentially that of the half-life

of circulating erythrocytes. The minimum interval following exposure to VIRAZOLE before pregnancy may be safely initiated is unknown (see Contraindications, Warnings, and Information for Health Care Personnel).

#### NURSING MOTHERS

VIRAZOLE has been shown to be toxic to lactating animals and their offspring. It is not known if VIRAZOLE is excreted in human milk.

#### INFORMATION FOR HEALTH CARE PERSONNEL

Health care workers directly providing care to patients receiving aerosolized VIRAZOLE should be aware that ribavirin has been shown to be teratogenic in all animal species in which adequate studies have been conducted (rodents and rabbits). Although no reports of teratogenesis in offspring of mothers who were exposed to aerosolized VIRASOLE during pregnancy have been confirmed, no controlled studies have been conducted in pregnant women. Studies of environmental exposure in treatment settings have shown that the drug can disperse into the immediate bedside area during routine patient care activities with highest ambient levels closest to the patient and extremely low levels outside of the immediate bedside area. Adverse reactions resulting from actual occupational exposure in adults are described below (see Adverse Events in Health Care Workers). Some studies have documented ambient drug concentrations at the bedside that could potentially lead to systemic exposures above those considered safe for exposure during pregnancy (1/1000 of the NOTEL dose in the most sensitive animal species). (7,8,9)

A 1992 study conducted by the National Institute of Occupational Safety and Health (NIOSH) demonstrated measurable urine levels of ribavirin in health care workers exposed to aerosol in the course of direct patient care. (7) Levels were lowest in workers caring for infants receiving aerosolized VIRAZOLE with mechanical ventilation and highest in those caring for patients being administered the drug via an oxygen tent or hood. This study employed a more sensitive assay to evaluate ribavirin levels in urine than was available for several previous studies of environmental exposure that failed to detect measurable ribavirin levels in exposed workers. Creatinine adjusted urine levels in the NIOSH study ranged from less than 0.001 to 0.140 uM of ribavirin per gram of creatinine in exposed workers. However, the relationship between urinary ribavirin levels in exposed workers, plasma levels in animal studies, and the specific risk of teratogenesis in exposed pregnant women is unknown.

It is good practice to avoid unnecessary occupational exposure to chemicals wherever possible. Hospitals are encouraged to conduct training programs to minimize potential occupational exposure to VIRAZOLE. Health care workers who are pregnant should consider avoiding direct care of patients receiving aerosolized VIRAZOLE. If close patient contact cannot be avoided, precautions to limit exposure should be taken. These include administration of VIRAZOLE in negative pressure rooms; adequate room ventilation (at least six air exchanges per hour); the use of VIRAZOLE aerosol scavenging devices; turning off the SPAG-2 device for 5 to 10 minutes prior to prolonged patient contact; and wearing appropriately fitted respirator masks. Surgical masks do not provide adequate filtration of VIRAZOLE particles. Further information is

available from NIOSH's Hazard Evaluation and Technical Assistance Branch and additional recommendations have been published in an Aerosol Consensus Statement by the American Respiratory Care Foundation and the American Association for Respiratory Care.(10)

## ADVERSE REACTIONS

The description of adverse reactions is based on events from clinical studies (approximately 200 patients) conducted prior to 1986, and the controlled trial of aerosolized VIRAZOLE conducted in 1989-1990. Additional data from spontaneous post-marketing reports of adverse events in individual patients have been available since 1986.

## DEATHS

Deaths during or shortly after treatment with aerosolized VIRAZOLE have been reported in 20 cases of patients treated with VIRAZOLE (12 of these patients were being treated for RSV infections). Several cases have been characterized as "possibly related" to VIRAZOLE by the treating physician; these were in infants who experienced worsening respiratory status related to bronchospasm while being treated with the drug. Several other cases have been attributed to mechanical ventilator malfunction in which VIRAZOLE precipitation within the ventilator apparatus led to excessively high pulmonary pressures and diminished oxygenation. In these cases the monitoring procedures described in the current package insert were not

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employed (see Description of Studies, Warnings, and Dosage and Administration).

## PULMONARY AND CARDIOVASCULAR

Pulmonary function significantly deteriorated during aerosolized VIRAZOLE treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

In the original study population of approximately 200 infants who received aerosolized VIRAZOLE, several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of VIRAZOLE in these events is indeterminate. Since the drug's approval in 1986, additional reports of similar serious, though non-fatal, events have been filed infrequently. Events associated with aerosolized VIRAZOLE use have included the following:

Pulmonary: Worsening of respiratory status, bronchospasm, pulmonary edema, hypoventilation, cyanosis, dyspnea, bacterial pneumonia, pneumothorax, apnea, atelectasis and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, bradycardia and digitalis toxicity. Bigeminy, bradycardia and tachycardia have been described in patients with underlying congenital heart disease.

Some subjects requiring assisted ventilation experienced serious difficulties, due to inadequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive and expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted. Measures to avoid these complications should be followed carefully (see Dosage and Administration).

#### HEMATOLOGIC

Although anemia was not reported with use of aerosolized VIRAZOLE in controlled clinical trials, most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Anemia has been shown to occur frequently with experimental oral and intravenous VIRAZOLE in humans. Also, cases of anemia (type unspecified), reticulocytosis and hemolytic anemia associated with aerosolized VIRAZOLE use have been reported through post-marketing reporting systems. All have been reversible with discontinuation of the drug.

#### OTHER

Rash and conjunctivitis have been associated with the use of aerosolized VIRAZOLE. These usually resolve within hours of discontinuing therapy. Seizures and asthenia associated with experimental intravenous VIRAZOLE therapy have also been reported.

#### ADVERSE EVENTS IN HEALTH CARE WORKERS

Studies of environmental exposure to aerosolized VIRAZOLE in health care workers administering care to patients receiving the drug have not detected adverse signs or symptoms related to exposure. However, 152 health care workers have reported experiencing adverse events through post-marketing surveillance. Nearly all were in individuals providing direct care to infants receiving aerosolized VIRAZOLE. Of 358 events from these 152 individual health care worker reports, the most common signs and symptoms were headache (51% of reports), conjunctivitis (32%), and rhinitis, nausea, rash, dizziness, pharyngitis, or lacrimation (10-20% each). Several cases of bronchospasm and/or chest pain were also reported, usually in individuals with known underlying reactive airway disease. Several case reports of damage to contact lenses after prolonged close exposure to aerosolized VIRAZOLE have also been reported. Most signs and symptoms reported as having occurred in exposed health care workers resolved within minutes to hours of discontinuing close exposure to aerosolized VIRAZOLE (also see Information for Health Care Personnel).

The symptoms of RSV in adults can include headache, conjunctivitis, sore throat and/or cough, fever, hoarseness, nasal congestion and wheezing, although RSV infections in adults are typically mild and transient. Such infections represent a potential hazard to uninfected hospital patients. It is unknown whether certain symptoms cited in reports from health care workers were due to exposure to the drug or infection with RSV. Hospitals should implement appropriate infection control procedures.

## OVERDOSAGE

No overdose with VIRAZOLE by aerosol administration has been reported in humans. The LD50 in mice is 2 gm orally and is associated with hypoactivity and gastrointestinal symptoms (estimated human equivalent dose of 0.17gm/kg, based on body surface area conversion). The mean plasma half-life after administration of aerosolized VIRAZOLE for pediatric patients is 9.5 hours. VIRAZOLE is concentrated and persists in red blood cells for the life of the erythrocyte (see Pharmacokinetics).

## DOSAGE AND ADMINISTRATION

BEFORE USE, READ THOROUGHLY THE VIRATEK SMALL PARTICLE AEROSOL GENERATOR (SPAG) MODEL SPAG-2 OPERATOR'S MANUAL FOR SMALL PARTICLE AEROSOL GENERATOR OPERATING INSTRUCTIONS. AEROSOLIZED VIRAZOLE SHOULD NOT BE ADMINISTERED WITH ANY OTHER AEROSOL GENERATING DEVICE.

The recommended treatment regimen is 20 mg/ml VIRAZOLE as the starting solution in the drug reservoir of the SPAG-2 unit, with continuous aerosol administration for 12-18 hours per day for 3 to 7 days. Using the recommended drug concentration of 20 mg/ml the average aerosol concentration for a 12 hour delivery period would be 190 micrograms/liter of air. Aerosolized VIRAZOLE should not be administered in a mixture for combined aerosolization or simultaneously with other aerosolized medications.

## NON-MECHANICALLY VENTILATED INFANTS

VIRAZOLE should be delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume and

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condensation area are larger in a tent and this may alter delivery dynamics of the drug.

## MECHANICALLY VENTILATED INFANTS

The recommended dose and administration schedule for infants who require mechanical ventilation is the same as for those who do not. Either a pressure or volume cycle ventilator may be used in conjunction with the SPAG-2. In either case, patients should have their endotracheal tubes suctioned every 1-2 hours, and their pulmonary pressures monitored frequently (every 2-4 hours). For both pressure and volume ventilators, heated wire connective tubing and bacteria filters in series in the expiratory limb of the system (which must be changed frequently, i.e., every 4 hours) must be used to minimize the risk of VIRAZOLE precipitation in the system and the subsequent risk of ventilator dysfunction. Water column pressure release valves should be used in the ventilator circuit for pressure cycled ventilators, and may be utilized with volume cycled ventilators (SEE SPAG-2 MANUAL FOR DETAILED INSTRUCTIONS).

## METHOD OF PREPARATION

VIRAZOLE brand of ribavirin is supplied as 6 grams of lyophilized powder per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with Sterile Water for Injection, USP, or Inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml SPAG-2 reservoir and further dilute to a final volume of 300 ml with Sterile Water for Injection, USP, or Inhalation. The final concentration should be 20 mg/ml. IMPORTANT: This water should NOT have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

## HOW SUPPLIED:

VIRAZOLE (ribavirin for inhalation solution) is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml Sterile Water for Injection or Sterile Water for Inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25 degrees C (59-78 degrees F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30 degrees C, 68-86 degrees F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

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\*Copies of the Report may be purchased from National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161; Ask for Publication PB 93119-345.

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