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APPLICATION FOR INCLUSION OF RIBAVIRIN IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

1. SUMMARY STATEMENT

This is a proposal to include ribavirin for treatment of viral haemorrhagic fevers (VHF), particularly Lassa fever, Argentine haemorrhagic fever (AHF), Crimean-Congo haemorrhagic fever (CCHF) and haemorrhagic fever with renal syndrome (HFRS), in the WHO Model List of Essential Medicines (1-5).

In 1972, Sidwell et al. (1) first reported that ribavirin, a broad-spectrum antiviral drug, was active against a variety of RNA and DNA viruses in culture and in animals, without undue toxicity. Since then, ribavirin has been found effective for the treatment of 1) respiratory syncytial virus (RSV) infection in immunosuppressed and high-risk children and adults, 2) viral haemorrhagic fevers (VHFs) caused by Arenaviridae and Bunyaviridae (Lassa, Junin, Crimean-Congo and Hantaan, a hanta virus) (1-5), and 3) hepatitis C virus (HCV) infection. Ribavirin has not been found effective for the treatment for hantavirus pulmonary syndrome (6), Rift Valley fever, or Filoviruses (7). While the exact mechanism of action is unknown, the drug appears to interfere with intracellular RNA- and DNA synthesis and subsequently inhibits protein synthesis and viral replication of ribavirin-sensitive RNA- or DNA viruses (8).

The United States Food and Drug Administration (FDA) has approved the use of ribavirin for treatment of respiratory syncytial virus and hepatitis C virus infection. There are no antiviral drugs approved by FDA for treatment of viral haemorrhagic fevers.

2. NAME OF THE FOCAL POINT IN WHO SUBMITTING THE APPLICATION

- Dr Cathy Roth, Coordinator, Biorisk Reduction for Dangerous Pathogens Team (BDP), Department of Epidemic and Pandemic Alert and Response (CDS/EPR)
- Dr Pierre Formenty, Project Leader for Dangerous Pathogens, CDS/EPR/BDP

3. ORGANIZATIONS CONSULTED FOR THE APPLICATION

- Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA
- Médecins sans Frontières (MSF), Paris, France, and Geneva, Switzerland
- Medical Emergency Relief International (Merlin), London, UK
- National Institute for Communicable Diseases (NICD), Johannesburg, South Africa
- Tulane School of Tropical Medicine, New Orleans, LA, USA
- United States Army Medical Research Institute of Infectious Diseases (USAMRIID), Frederick, MD, USA

4. INTERNATIONAL NONPROPRIETARY NAME (INN, GENERIC NAME) OF THE MEDICINE

Ribavirin, chemically denoted as 1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide.

5. FORMULATION PROPOSED FOR INCLUSION (INCLUDING ADULT AND PAEDIATRIC)

In the United States, ribavirin is FDA-approved and marketed 1) as inhalation solution (Virazole®, ICN / Valeant) for treatment of RSV infection, and 2) as oral capsule (Rebetol®, Essex-Schering-Plough) and tablet (Copegus®, Roche; Ribasphere 200 mg / Ribapak 400 mg, 600 mg, Three Rivers Pharmaceutical Industries / Par Pharmaceuticals) for treatment of hepatitis C virus infection. Ribavirin for intravenous administration (Virazole®) is of limited availability, produced by ICN / Valeant for compassionate use under an investigational new drug (IND) application (7). Ribavirin for intravenous administration is supplied in vials containing 1000 mg and 800 mg of ribavirin dissolved in 10mL phosphate buffer solution. Ribavirin for oral administration is supplied in capsules or film-coated tablets containing 200 mg. The only present FDA-approved indication for these products is in conjunction with interferon against chronic hepatitis C with hepatic damage and inhalation solution for treatment of RSV.

The patent for ribavirin in the United States expired in September 2001. Production and sale of generic ribavirin started in 2005 (Three Rivers Pharmaceutical Industries / Par Pharmaceuticals, Sandoz, Teva Pharmaceutical Industries, and Warrick Pharmaceuticals (generic arm of Schering-Plough)).

6. INTERNATIONAL AVAILABILITY - MANUFACTURERS

- Chengdu Diao Group JiuHong Pharmaceutical Co., Ltd, Chengdu, Sichuan, People's Republic of China
- China National Medicines Guorui Pharmaceutical Co., Ltd, Beijing, People's Republic of China
- Essex-Schering-Plough Pharmaceuticals, Kenilworth, NJ, USA.
- Hoffmann-La Roche Ltd, Basel, Switzerland.
- ICN Pharmaceuticals / Valeant Pharmaceuticals International, Costa Mesa, CA, USA
- Jiangsu Lianshui Pharmaceutical Co., Ltd, Lianshui, Jiangsu, People's Republic of China
- Kunming Pharmaceutical Co., Ltd, Kunming, Yunnan, People's Republic of China
- Lokis Pharmaceutical (Jilin) Co., Ltd, Meihekou, Jilin, People's Republic of China
- Qianjiang Pharmaceutical Co., Ltd, Qianjiang, Hubei, People's Republic of China
- Shandong Xinhua Pharmaceutical Co., Ltd, Zibo, Shandong, People's Republic of China
- Siping Juneng Pharmaceutical Co., Ltd, Siping, Jilin, People's Republic of China
- Szyy Group Pharmaceutical Co., Ltd, Jiangyan, Jiangsu, People's Republic of China
- Three Rivers Pharmaceuticals, Cranberry Township, PA, USA
- Yanzhou Yijian Pharmaceutical Co., Ltd, Yanzhou, Shandong, People's Republic of China
- Zhejiang Zhebei Pharmaceutical Co., Ltd, Deqing Xinshi, Zhejiang, People's Republic of China

7. LISTING REQUESTED

Listing requested as individual medicine.

8. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE (epidemiological information on disease burden, assessment of current use, target population)

Lassa fever ("Old World" Arenaviridae)

Lassa virus haemorrhagic fever is an acute illness that occurs in West Africa (7). The virus is a single-stranded RNA virus belonging to the virus family Arenaviridae. Lassa fever is known to be endemic in Guinea (Conakry), Liberia, Sierra Leone and parts of Nigeria, but probably exists in other West African countries as well. Some studies indicate that 300 000 to 500 000 cases of Lassa fever and 5000 deaths occur yearly across West Africa (7, 9). The overall case-fatality rate is 1%-2% in the community, up to 15%-25% among hospitalized patients, and up to 50%-60% during outbreaks (9). Deafness has been documented in more than 25%-30% of the patients that have recovered. Death usually occurs within 14 days of onset in fatal cases. The disease is especially severe late in pregnancy, with maternal death or fetal loss occurring in over 80% of cases during the third trimester (10, 11).

Argentine haemorrhagic fever ("New World" Arenaviridae)

Argentine haemorrhagic fever (AHF) is transmitted by rodents and caused by Junin virus, a member of the Arenaviridae family. Since the disease was first recognized in 1955, annual outbreaks have been notified without interruption, with more than 24.000 cases reported in 1993 (7, 12-14). The endemo-epidemic area of the disease is located in the humid pampa, the most fertile farm land of Argentina (15). AHF is a serious acute viral disease characterized by a febrile syndrome with haematological, neurological, renal and cardiovascular alterations. Without treatment, case-fatality ratio is 15-30% (15).

Since 1992, an attenuated live vaccine against AHF has been available. The vaccine has been used in high-risk adult populations with a significant reduction in the incidence of the disease. However, even with an effective vaccine, sporadic cases and outbreaks continue to occur. The early treatment with AHF convalescent plasma is extremely effective and reduces mortality to 1%. However, this treatment is only effective if given during the first 8 day-period after onset of symptoms. In addition plasma therapy entails risk of transfusion-borne diseases and the presentation of a late neurologic syndrome (LNS) that has been occurred in 10% of treated survivors (7, 12-14).

Crimean-Congo haemorrhagic fever (Bunyaviridae)

The Crimean-Congo haemorrhagic fever (CCHF) virus belongs to the Bunyaviridae family of viruses (7, 16). CCHF is a zoonosis transmitted by ticks that results in severe outbreaks in humans but which is not pathogenic for ruminants, their amplifier host. Although CCHF virus is not pathogenic in animals, the disease is known as one of the most important VHFs because of its high case fatality ratio (10-40%) and its potential for nosocomial transmission. CCHF is endemic throughout Africa, the Balkans, the Middle East and Asia south of 50° latitude north, the limit of its tick reservoir, the genus *Hyalomma* (16).

Reports of sporadic human cases and limited outbreaks are increasing every year. Recently outbreaks of CCHF in Afghanistan (2001-2006), Iran (2001), Kazakhstan (2005), Kosovo (2001), Mauritania (2002-2003), Pakistan (2001-2006), Russia (2006), Senegal (2004 with one human case imported to France), South Africa (2006), Sudan (2004), Tajikistan (2002-2004), and Turkey (2003-2006) have drawn international attention to this emerging problem. In these endemic areas, ecological changes, poverty and social instability, insufficient medical equipment together with absence of infection control standard precautions have all contributed to the increased transmission of the CCHF virus in its natural environment, in the community or in hospital settings. Absence of available and affordable therapy still limits outbreak control activities.

Haemorrhagic fever with renal syndrome (Bunyaviridae)

Haemorrhagic fever with renal syndrome (HFRS) is a group of clinically similar illnesses caused by hantaviruses from the Bunyaviridae family of viruses(7, 17). HFRS includes diseases such as Korean haemorrhagic fever, epidemic haemorrhagic fever, and nephropathis epidemica. The viruses that cause HFRS include Hantaan, Dobrava-Belgrade, Seoul, and Puumala. HFRS is found throughout the world. Haantan virus is widely distributed in eastern Asia, particularly in China, Russia, and on the Korean peninsular. Puumala virus is found in Scandinavia, western Europe, and Russia. Dobrava virus is found primarily in the Balkans, and Seoul virus is found worldwide.

9. TREATMENT DETAILS (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

Lassa fever, Argentine- and Crimean-Congo haemorrhagic fevers: adults (including pregnant women- see also "contraindications" (application #11 and 16, appendices 2 and 3)

| Administration | Loading dose d1 | d1-4 | d5-10 |
|----------------|---|---|---------------------------------------|
| IV (6) | 17 mg/kg (max 1000 mg per dose) 1x * | 17 mg/kg (max 1000 mg per dose) q 6h | 8 mg/kg (max 500 mg per dose) q 8h |
| PO (4) | 2000 mg 1x | 1000 mg q 6h | 500 mg q 6h |

* The loading dose for intravenous ribavirin has been suggested in other reports to be 30 mg/kg (max 2000 mg per dose) for Lassa fever (6, 7), and 34 mg/kg for AHF (13).

Lassa fever, Argentine- and Crimean-Congo haemorrhagic fevers: children

| Administration | Loading dose d1 | d1-4 | d5-10 |
|----------------|-----------------|---------------|--------------|
| IV (6) | 17 mg/kg 1x | 17 mg/kg q 6h | 8 mg/kg q 8h |
| PO (4) | 30 mg/kg 1x | 15 mg/kg q 6h | 7 mg/kg q 6h |

Oral ribavirin treatment of CCHF reported by Fisher-Hoch et al. (18): 4000 mg/d d1-4, 2400 mg/d d5-10.

Haemorrhagic fever with renal syndrome (HFRS): adults

| Administration | Loading dose d1 | d1-4 | d5-10 |
|----------------|-----------------|---------------|--------------|
| IV (19) | 33 mg/kg 1x | 16 mg/kg q 6h | 8 mg/kg q 8h |

10. SUMMARY OF COMPARATIVE EFFECTIVENESS IN A VARIETY OF CLINICAL SETTINGS

Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Search of Medline and Cochrane Library as of 16 October 2006 (Keywords: ribavirin, injections, Lassa fever/complications/*drug therapy, Ribavirin/*adverse effects, Crimean-Congo haemorrhagic fever, haemorrhagic fever with renal syndrome, viral haemorrhagic fevers).

Summary of available data (appraisal of quality, outcome measures, summary of results) Summary of available estimates of comparative effectiveness

Lassa fever

In a prospective study of Lassa fever in Sierra Leone, McCormick et al. (4) identified variables associated with high risk of death and evaluated the efficacy of ribavirin (intravenous and oral administration) and Lassa virus-convalescent plasma for the treatment of Lassa fever. The authors concluded that ribavirin was effective in the treatment of Lassa fever and should be used at any point in the illness, though preferably during the first six days after onset (4, 20).

Argentine haemorrhagic fever ("New World" Arenaviridae)

There are only few animal and human studies on the clinical effectiveness of ribavirin in the treatment of New World Arenaviridae (7, 12-14). These limited clinical data indicate a clear benefit of ribavirin treatment, with good tolerability and safety of the drug (7, 12-14).

Crimean-Congo haemorrhagic fever

There is currently no specific antiviral therapy for CCHF. However, ribavirin has been shown to inhibit in-vitro viral replication in Vero cells (24) and reduced the mean time to death in a suckling mouse model of CCHF (25). Additionally, several case reports have been published that suggest oral or intravenous ribavirin is effective for treating CCHF infections (18, 26-28). All published reports showed a clear benefit in patients with confirmed CCHF treated with ribavirin (intravenous and oral administration). There were no major side effects or mortality associated with ribavirin treatment (18, 24, 25, 27, 29, 30). The results of all these studies are limited by their design and sample size.

Haemorrhagic fever with renal syndrome

Ribavirin was demonstrated to have anti-hantaviral effect both in vitro and in vivo. Ribavirin is often used in treatment of HFRS in China and clinical trials have shown that ribavirin therapy can significantly reduce HFRS-associated mortality.

Huggins et al. (19) carried out a prospective, randomized, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin in 242 patients with serologically confirmed haemorrhagic fever with renal syndrome (HFRS) in the People's Republic of China. Mortality was significantly reduced (sevenfold decrease in risk) among ribavirin-treated patients. Ribavirin therapy resulted in a significant risk reduction of entering the oliguric phase and experiencing haemorrhage. The only ribavirin-related side effect was a fully reversible anaemia after completion of therapy. The effectiveness of ribavirin therapy for HFRS was also demonstrated by different Chinese investigators (Luo et al. (31) and Liu et al. (32)).

11. SUMMARY OF COMPARATIVE EVIDENCE ON SAFETY

Estimate of total patient exposure to date

The safety of oral ribavirin has been examined in approximately 5000-10 000 patients with VHFs in controlled and uncontrolled clinical trials. Ribavirin was generally well tolerated (20).

Description of adverse effects/reactions

Intravenous ribavirin

Haemolytic anaemia has been the most frequently reported side effect. Ribavirin administered as an intravenous bolus has been reported to induce rigors; consequently, it is recommended that the drug be administered as an infusion over 10-15 minutes. There have been reports of pancytopenia and pancreatitis associated with use of intravenous ribavirin. As these patients had multiple health problems and were receiving other medications, there were other potential causes for those events.

Oral ribavirin

The most common side effect of ribavirin is a mild to moderate but fully reversible haemolytic anaemia. In clinical trials the mean haemoglobin level of patients treated with ribavirin fell by approximately 2 g/dL over the first 4 weeks of treatment. The fall in haemoglobin was accompanied by elevation of bilirubin level and a compensatory reticulocytosis. After 4 weeks the parameters remained at approximately the same levels for the remainder of the treatment period. Following completion of the course of treatment, these laboratory values returned to pre-treatment levels. Anaemia associated with ribavirin therapy is often asymptomatic and can be managed by monitoring blood count and serum biochemistry.

The list of adverse effects described in the eModel formulary is sufficient.

Contra-indications and precautions

Ribavirin is contraindicated for treatment of hepatitis c virus infection in women or girls who are or may become pregnant during treatment. However, for treatment of VHF, the benefit of ribavirin therapy appears to outweigh any fetal risk. Given the high risk of Lassa-related mortality, AHF- and CCHF-related mortality both for pregnant women and foetuses, ribavirin still is recommended (7). Ribavirin is contraindicated for pregnant or nursing mothers given the low disease mortality of HFRS and the known teratogenic potential of ribavirin.

Ribavirin has demonstrated significant teratogenic and 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 ribavirin may cause fetal harm in humans. Due to the long terminal half-life of elimination of the drug, the minimum interval following treatment with ribavirin before pregnancy can be safely initiated is estimated to be 7 months.

Ribavirin is contraindicated in patients with chronic anaemia and haemoglobin levels below 8 g/dl, and in patients with severe renal impairment (creatinine clearance <30 ml/min). The pharmacokinetics of ribavirin in subjects with decompensated liver disease appears to be similar to that of healthy volunteers. However, the drug may accumulate in patients with impaired renal function. These patients should be carefully monitored during therapy with ribavirin for signs and symptoms of toxicity, such as anaemia.

Ribavirin is also contraindicated in individuals who show hypersensitivity to the drug or its components.

Identification of variation in safety due to health systems and patient factors

Ribavirin should not be administered in anaemia with haemoglobin levels <8 g/dl.

Summary of comparative safety against comparators

None known.

12. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS WITHIN THE PHARMACOLOGICAL CLASS OR THERAPEUTIC GROUP**Range of costs of ribavirin, USA and China, October 2006****Oral ribavirin administration**

| Manufacturer | Strength [mg] | Number of tablets / package | Price / package | Price for 10-day PO treatment |
|---|----------------------|------------------------------------|------------------------|--------------------------------------|
| Rebetol®, Schering-Plough | 200 | 30 | \$553.99 | \$2,769.95 |
| Ribasphere®, Three Rivers / Par | 200 | 30 | \$280.00 | \$1,400.00 |
| Copegus®, Hoffmann-La Roche | 200 | 168 | \$1'424.02 | \$1,271.45 |
| Generic, USA | 200 | 56 | \$318.42 | \$852.91 |
| Zhejiang Zhebei Pharmaceutical Co., Ltd | 100 | 24 | \$1.33 | \$16.63 |
| China National Medicines Guorui Pharmaceutical Co., Ltd | 100 | 24 | \$1.33 | \$16.63 |
| Szyy Group Pharmaceutical Co., Ltd | 50 | 24 | \$1.03 | \$25.75 |
| Chengdu Diao Group Jihong Pharmaceutical Co., Ltd | 50 | 24 | \$0.59 | \$14.75 |
| Shandong Xinhua Pharmaceutical Co., Ltd | 20 | 100 | \$0.91 | \$13.65 |

Intravenous ribavirin administration

| Manufacturer | Strength [mg / ml] | Number of vials / package | Price / package | Price / 100 mg | Price for 10-day IV treatment ^α |
|---|--------------------|---------------------------|-----------------|----------------|--|
| Virazole® (Valeant) IV ^β | 100 | 10 | \$134.00 | \$13.40 | \$3,886.00 |
| Shandong Xinhua Pharmaceutical Co., Ltd | 100 | 10 | \$0.76 | \$0.08 | \$22.04 |
| Jiansu Lianshui Pharmaceutical Co., Ltd | 100 | 10 | \$0.76 | \$0.08 | \$22.04 |
| Kunming Pharmaceutical Co., Ltd | 100 | 10 | \$0.76 | \$0.08 | \$22.04 |
| Qianjiang Pharmaceutical Co., Ltd | 100 | 10 | \$0.76 | \$0.08 | \$22.04 |
| Shandong Tianfu Pharmaceutical Co., Ltd | 100 | 10 | \$0.70 | \$0.07 | \$20.30 |
| Yanyhou Yijian Pharmaceutical Co., Ltd | 100 | 5 | \$0.24 | \$0.05 | \$13.92 |
| Lokis Pharmaceutical (Jilin) Co., Ltd | 100 | 1 | \$0.04 | \$0.04 | \$12.47 |

^α For calculating the treatment costs resulting from IV administration of ribavirin, we have assumed a male adult person of 70kg weight.

^β IV-formulation is not commercially available, and can only be purchased in bulk for investigational new drug (IND) use, or self-prepared from commercially available inhalation solution.

13. COMPARATIVE COST-EFFECTIVENESS PRESENTED AS RANGE OF COST PER ROUTINE OUTCOME (e.g. , cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

Please refer to #12, tables, last column, price of 10-day oral- vs. IV-treatment.

14. SUMMARY OF REGULATORY STATUS OF THE MEDICINE (in country of origin, and preferably in other countries as well)

- USA–Phase IV
- People’s Republic of China–Phase IV
- Switzerland–Phase IV

15. AVAILABILITY OF PHARMACOPOEIAL STANDARDS (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

Ribavirin is listed in all major pharmacopoeias.

16. PROPOSED NEW TEXT FOR THE WHO MODEL FORMULARY

The optimal route of administration of ribavirin is by mouth. However, given the potential need for parenteral drug administration, an IV formulation is also available.

For adults (including pregnant women - see also "contraindications") with Lassa fever, AHF, or CCHF, administration by PO is given in decreasing interval dosings over ten days. The loading dose on Day 1 is a one time oral dose of 2000 mg, followed on Days 1-4 with 1000 mg every 6 hours orally, and then followed on Days 5-10 with 500 mg every 6 hours orally. For adults (including pregnant women - see also "contraindications") with Lassa fever, AHF or CCHF that require IV administration, the following is given in decreasing interval dosings. The loading dose on Day 1 is a one time IV dose of 17 mg/kg (max 1000 mg per dose), followed on Days 1-4 with 17 mg/kg (max 1000 mg per dose, every 6 hours IV, and then followed on Days 5-10 with 8 mg/kg (max 500 mg per dose) every 8 hours IV.

For children with Lassa fever, AHF, or CCHF, administration by PO is given in decreasing interval dosings over ten days. The loading dose on Day 1 is a one time oral dose of 30 mg/kg, followed on Days 1-4 with 15 mg/kg every 6 hours orally, and then followed on Days 5-10 with 7 mg/kg every 6 hours orally. For children with Lassa fever, AHF or CCHF that require IV administration, the following is given in decreasing interval dosings. The loading dose on Day 1 is a one time IV dose of 17 mg/kg, followed on Days 1-4 with 17 mg/kg every 6 hours IV, and then followed on Days 5-10 with 7 mg/kg every 8 hours IV.

For adults with haemorrhagic fever with renal syndrome (HFRS), the following is given in decreasing interval dosings. The loading dose on Day 1 is a one time IV dose of 33 mg/kg (max 1000 mg per dose), followed on Days 1-4 with 16 mg/kg (max 1000 mg per dose, every 6 hours IV, and then followed on Days 5-10 with 8 mg/kg (max 500 mg per dose) every 8 hours IV. Ribavirin is contraindicated for pregnant or nursing mothers given the low disease mortality of HFRS and the known teratogenicity potential of ribavirin.

Information: Take the oral preparation with food. Monitor CBC at least weekly.

Ribavirin is contraindicated in patients who have a hypersensitivity to this drug, class, or components.

Ribavirin is contraindicated in patients with a haemoglobin level less than 8 g/dl.

Ribavirin is contraindicated in patients with renal insufficiency that has a creatinine clearance (CrCl) less than 30 ml/min.

Ribavirin is contraindicated in patients with autoimmune hepatitis or decompensated liver disease.

Ribavirin is contraindicated in patients with significant or unstable cardiac disease, with haemoglobinopathies.

Ribavirin is contraindicated in pregnancy for the treatment of Hepatitis C and HFRS (low mortality) as there is positive evidence of serious fetal abnormalities in animals, humans, or both. Maternal benefit will need to be considered given the severe fetal risks when using ribavirin for haemorrhagic fevers. Lassa fever is especially severe late in pregnancy, with maternal death and/or fetal loss occurring in greater than 80% of cases during the third trimester. There is available animal and human data that demonstrates potential or actual adverse effects to infant and breast milk.

Serious Reactions can include haemolytic anaemia, neutropenia, thrombocytopenia, aplastic anaemia, teratogenicity, embryocide, severe infection, severe depression, suicidal ideation, autoimmune disorders, pulmonary toxicity, pancreatitis, diabetes, hypothyroidism, hyperthyroidism, myocardial infarction, arrhythmias, colitis, retinal haemorrhage, retinal thrombosis, or rarely, hypersensitivity reactions.

Common Reactions can include fatigue, headache, fever, rigors, myalgias, arthalgias, anxiety, irritability, insomnia, alopecia, neutropenia, nausea, vomiting, anorexia, depression, pruritis, dizziness, dyspnoea, anaemia, diarrhea, impaired concentration, cough, rash, or thrombocytopenia.

Metabolism is via the CYP450 system. Excretion is 61% urine and 12% feces. The half-life is 120-170 hours. While the exact mechanism of action is unknown, the drug appears to interfere with intracellular RNA and DNA synthesis and subsequently inhibit protein synthesis and viral replication of ribavirin-sensitive RNA or DNA viruses.

Ribavirin requires a prescription. It is not a controlled substance.

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ABBREVIATIONS USED

| | |
|--------------------|--|
| AHF | Argentine haemorrhagic fever |
| ALT | Serum alanine aminotransferase |
| AST | Serum aspartate aminotransferase |
| AST/ALT ratio | Ratio of serum aspartate aminotransferase to serum alanine aminotransferase |
| CCHF | Crimean-Congo haemorrhagic fever |
| d | day |
| FDA | US Food and Drug Administration |
| HFRS | Haemorrhagic fever with renal syndrome |
| h | hour |
| H(C)PS | Hanta (cardio-)pulmonary syndrome |
| IC | Intracerebral |
| IND | Investigational new drug |
| IP | Intraperitoneal |
| IU | International Unit |
| IUPAC | International Union of Pure and Applied Chemistry |
| IV | Intravenous administration |
| LLC | Limited liability company |
| MTD | Mean time to death |
| OD | Optical density |
| PEP | Post-exposure prophylaxis |
| PO | Per os, oral administration |
| q | <i>Quaque</i> , Latin abbreviation for interval at which medication is administered (e.g., q 6h→every 6 hours) |
| q.d. | <i>Quaque die</i> , Latin abbreviation for "given every day," or "daily" |
| TCID ₅₀ | Tissue Culture Infecting Dose |
| VHF | Viral haemorrhagic fever |

**APPENDIX 1. PARTIAL LIST OF COUNTRIES WITH REGULATORY PROCESSES FOR
RIBAVIRIN**

Australia
Brazil
Canada
Federal Republic of Germany
India
People's Republic of China
Switzerland
United Kingdom
United States of America

Please note : Appendices 2 and 3 are for reference only and have been published by the manufacturers for different indications (RSV-, HCV-infections). We have elaborated for this application specific recommendations on indication and dosage for VHF, along with corresponding contraindications.

APPENDIX 2. PRESCRIBING INFORMATION: VIRAZOLE® (VALEANT), (RIBAVIRIN FOR INHALATION SOLUTION), RX ONLY

PDR PDR-DOC PDR Monograph Drug 84270800 5972 English En 5972 ANTI-INFECTIVE AGENTS, SYSTEMIC ANTIVIRALS NUCLEOSIDE ANALOGUES ANTIVIRALS(ANTI-INFECTIVE AGENTS, SYSTEMIC) ANTIVIRALS -- see under ANTIVIRALS(ANTI-INFECTIVE AGENTS, SYSTEMIC) HERPES TREATMENT -- see under ANTIVIRALS(ANTI-INFECTIVE AGENTS, SYSTEMIC) NUCLEOSIDE ANALOGUES Prescribed 8427 VALEANT PHARMACEUTICALS INTERNATIONAL Valeant PDR Virazole for Inhalation Solution Infections, lower respiratory tract, RSV-induced Respiratory syncytial virus (RSV) infections Pregnancy Retinal vascular disorder Hypogonadism Digitalis toxicity Cyanosis Fetal harm Muscle atrophy Convulsions Bigeminy Conjunctivitis Bradycardia Brain syndrome, acute Tachycardia Weakness Asthenia Rash Hypotension Blood pressure, reduction Anemia Anemia, hemolytic Underventilation Hypoventilation Apnea Atelectasis Death, infants Respiratory distress Pulmonary function, changes Reticulocytosis Carcinoma, skin, benign Bronchospasm Pain, chest Cardiac arrest Ventilator dependence Pneumothorax Pneumonia Edema, pulmonary Pulmonary edema Breathing, difficult Dyspnea Breathing, labored RIBAVIRIN Virazole for Inhalation Solution PDR® entry for

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

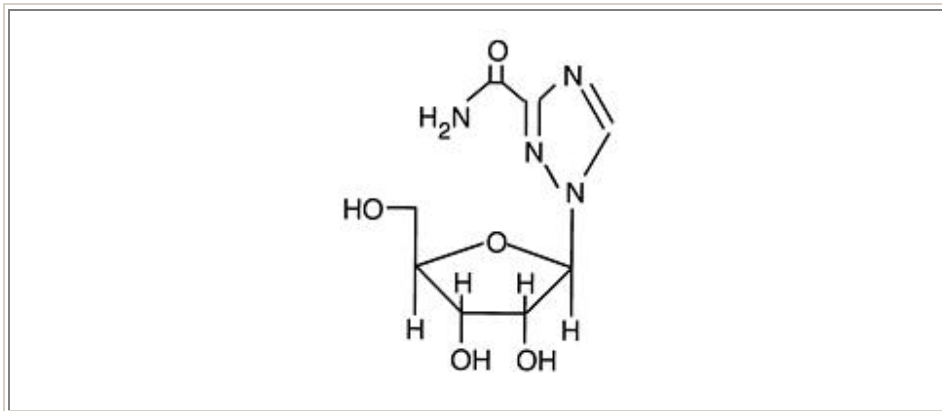
LESIONS IN RODENTS AND TO BE TERATOGENIC IN ALL ANIMAL SPECIES IN WHICH ADEQUATE STUDIES HAVE BEEN CONDUCTED (RODENTS AND RABBITS); (SEE CONTRAINDICATIONS).

DESCRIPTION

Virazole® 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 300 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:

Chemical Structure



Ribavirin is a stable, white crystalline compound with a maximum solubility in water of 142 mg/mL at 25°C and with only a slight solubility in ethanol. The empirical formula is C₈H₁₂N₄O₅ 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 µg/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 μM , with a mean concentration of 0.76 μM . 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 μM , with a mean concentration of 6.8 μM .

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 ELISA⁵ 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) and duration of required supplemental oxygen (8.7 vs 13.5 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 F₁O₂ 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 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

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 0.03-5.0 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 0.12 and 0.14 mg/kg, based on body surface area adjustment for the 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 oral 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 µM [0.024-0.049 µg/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 µM; 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 VIRAZOLE 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 µM 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 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 end 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 overdosage with VIRAZOLE by aerosol administration has been reported in humans. The LD₅₀ in mice is 2000 mg orally and is associated with hypoactivity and gastrointestinal symptoms (estimated human equivalent dose of 0.17 g/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 ICN SMALL PARTICLE AEROSOL GENERATOR 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 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, reconstitute drug with a minimum of 75 mL of sterile USP water for injection or inhalation in the original 100 mL glass vial. Shake well. 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, USP) is supplied in four packs containing 100 mL glass vials with 6 grams of Sterile, lyophilized drug (NDC 0187-0007-14) 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 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°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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APPENDIX 3. PRESCRIBING INFORMATION: REBETOL® (RIBAVIRIN, USP) CAPSULES

APPENDIX 4. DETAILS OF CLINICAL STUDIES AVAILABLE ON RIBAVIRIN THERAPY

Lassa fever ("Old World" Arenaviridae)

| Study | Methods | Participants | Interventions | Outcomes | Notes |
|---------------------------|---|---|---|---|---|
| McCormick et al. 1986 (4) | Case-control study, followed by prospective clinical trial. | 441 patients with confirmed Lassa virus infection, Sierra Leone | IV ribavirin vs. IV ribavirin+convalescent plasma | Mortality 55% (33/60, untreated) vs. 5% (1/20, treated within first 6 days, $p=0.0002$). | Risk factors ↑mortality: AST \geq 150IU, TCID ₅₀ \geq 10 ^{3.6} , treatment after first 6d- |

Argentine haemorrhagic fever ("New World" Arenaviridae)

| Study | Methods | Participants | Interventions | Outcomes | Notes |
|---------------------|----------------------------|---|--|--|-------|
| McKee et al. (22) | In vivo animal model study | Monkeys infected with Junin virus | Prophylactic schedule: Ribavirin 60 mg/kg 4d, 30 mg/kg for 3.5d and 11 mg/kg for 11d Treatment Schedule: d6 after inoculation, 60 mg/kg 3.5d, then 15 mg/kg for 11d. | All sham-treated controls monkeys died; those given prophylactic treatment seroconverted, but failed to develop viraemia or clinical illness; those who received therapeutic treatment showed transient viraemia. | |
| Remesar et al. (23) | In vivo animal model study | 10-day-old and 2-day-old rats infected with Junin virus | 10-day-old rats i.c. single dose of ribavirin 2h prior to virus inoculation i.c.; 2-day-old rats i.p. max 5 doses of ribavirin at 24h intervals, starting 2h prior to virus inoculation i.p. | No survival in controls; 60 mg and 90 mg doses led to 40% survival among 10-day-old rats at the end of observation period without delay in mean time to death (MTD); survival reached 73% in treated vs 22% in control groups, with 9.4-day delay in MTD | |
| Kenyon et | In vivo animal | Guinea pigs | Ribavirin was injected | Ribavirin treatment did not enhance | |

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| al. (21) | model study | infected with Junin virus | s.c. q.d. 45 mg/kg on the day before inoculation continued for 14d | survival of animals, but significantly increased the mean time to death (25.9±0.6 and 15.7±1.4 respectively) | |
| Enria et al. (13) | Prospective clinical study | Six confirmed cases of AHF, Argentina | Intravenous Ribavirin given at 34 mg/kg loading dose, followed by 17 mg/kg q 6h for 4d, then 8 mg/kg q 8h for 6d | Three patients survived; virus isolation became negative 3d after beginning treatment in all six patients | Side effects: Drop of haematocrit and haemoglobin on d5-6. Limitations: Small sample size, without controls |
| Enria et al. (14) | Placebo-controlled, prospective study | 18 confirmed cases of AHF, Argentina | Intravenous Ribavirin given at 34 mg/kg loading dose, followed by 17 mg/kg q 6h for 4d, then 8 mg/kg q 8h for 6d | Mortality in the Ribavirin and placebo groups were 12.5%(1/8) and 40%(4/10) respectively; Clearance of viraemia with 4 days after beginning treatment | Side effect: anaemia Limitations: Small sample size |

Crimean-Congo haemorrhagic fever (Bunyaviridae)

| Study | Methods | Participants | Interventions | Outcomes | Notes |
|--------------------|----------------------------|---|---|--|-------|
| Watts et al. (24) | In vitro study | African green monkey kidney Vero clone 76 cells (ATCC-CRL-1587) | Vero cell monolayers inoculated with CCHF virus were incubated with ribavirin of different concentrations | Ribavirin doses as low as 5 µg/ml caused a transient reduction of viral yields; A dose of 25 µg/ml induced further viral yields, and no evidence viral yields was demonstrated in cells treated with 50 or 250 5 µg/ml ribavirin | |
| Tignor et al. (25) | In vivo animal model study | Infant mice | Infant mice intraperitoneally infected with CCHF | Ribavirin treatment significantly reduced infant mouse mortality, decreased viraemia, and prolonged mean time to | |

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|-------------------------|-------------------------|--|---|--|--|
| | | | virus were treated with ribavirin | death | |
| Fisher-Hoch et al. (18) | Case study | 3 health workers with severe, serologically confirmed CCHF, Pakistan | Ribavirin orally administered at doses of 4 g/day for 4d and then 2.4 g/day for 6 days | All the three patients fully recovered | Limitations: Small sample size, without controls |
| Mardani et al. (27) | Historical cohort study | 187 suspected CCHF cases, 139 treated with ribavirin and 48 as historical controls, of which 81 cases were serologically confirmed, Iran | Ribavirin orally administered within a mean of 4d of on set at the doses of 30 mg/kg as a loading dose , 15 mg/kg q 6h for 4d and 7.5 mg/kg q 8h for 6 days | The fatalities among ribavirin recipients and historical controls for suspected patients were 30.2% and 45.8%, respectively; and those for confirmed patients were 11.6% and 58.3%, respectively | Limitations: Study design was neither randomized, nor placebo-controlled |
| Ergonul et al. (29) | Observational study | 35 serologically confirmed CCHF cases, with 8 cases ribavirin treated, Turkey | Ribavirin orally administered within a mean of 5.5d of on set at the doses of 4g q.d. for 4 days, and 2.4 g q.d. for 6 days | All the 8 severe cases treated with ribavirin survived, while 1 of 22 severe cases who did not receive ribavirin treatment died with a case-fatality of 4.5% | Limitations: Small sample size and non-randomized, non-placebo controlled |
| Ozkurt et al. (30) | Observational study | 60 CCHF cases of which 22 were treated with ribavirin and 38 were as historical controls, | Ribavirin orally administered immediately after admission at an initial loading dose of 2 g, then 1 g q 4h for 4 days, and | Case-fatality rate was 9.0%(1/22) in the ribavirin group vs. 10.5% (4/38) in the control group (P=0.85); The mean hospitalization time was 7.7d in the ribavirin group and 10.3d in control group (P=0.06) | Limitations: Small sample size and non-randomized, non-placebo controlled; |

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| | | Turkey | then 500 mg q 6h for 6 days | | One mild case of haemolytic anaemia recorded |
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Haemorrhagic fever with renal syndrome (HFRS)

| Study | Methods | Participants | Interventions | Outcomes | Notes |
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| Luo et al. (31) | Placebo controlled study | 72 cases of serologically confirmed HFRS patients within 5d of onset, PR China | Intravenous ribavirin: 10-15 mg/kg ribavirin in 200 ml of 10% glucose solution, once per day for 3 days. | All patients survived in ribavirin (38) and placebo (34) groups; 3.05±1.16 and 4.48±2.93d of fever duration; 3.73±1.26 and 5.0±2.14dto clearance of urine proteins in ribavirin and control groups respectively. | No apparent side effects recorded. Article in Chinese |
| Liu et al. (32) | Placebo controlled study | 64 cases of serologically confirmed HFRS patients within 5d of onset, PR China | Intravenous ribavirin: 500 mg ribavirin in 250-500 ml of 10% glucose solution, once per day for 3 days. | No death in ribavirin recipients (33 cases), while 2 deaths in placebo recipients (2/31); Severe complications in 9.1% and 32.3% of ribavirin recipients and placebo recipients respectively; 4.41 and 7.3dto the clearance of urine proteins in ribavirin recipients and placebo recipients respectively. | No apparent side effects recorded. Article in Chinese |
| Huggins et al. (19) | Randomized double-blind placebo-controlled study | 242 cases of HTNV IgM-confirmed HFRS patients within 4-6d of onset, PR China | Intravenous ribavirin: Loading dose of 33 mg/kg, 16 mg/kg q 6h for 4 days, and 8 mg/kg q 8h for 3d | 2.4% and 8.5% fatality rates in ribavirin recipients and placebo recipients respectively(P=0.01); Significant reduction in risk of entering the oliguric phase and experiencing haemorrhage in ribavirin group. | Reversible anaemia was the only observed side effect. |
| Yang et al. (33) | Randomized double-blind placebo-controlled | 52 cases of HTNV IgM- and virus positive HFRS patients | Intravenous ribavirin: Loading dose of 33 mg/kg, 16 mg/kg q | 3.6±0.2 and 6.9±0.6d of viraemia duration in ribavirin and placebo groups, respectively; Viral antigen OD value and virus | |

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| | study | within 4-6d of onset, PR China | 6h for 4 days, and 8 mg/kg q 8h for 3 days | infectivity titre of ribavirin group lower than that of placebo group. | |
|--|-------|--------------------------------|--|--|--|