1 NAME OF THE MEDICINAL PRODUCT:

Virazole (Ribavirin) Aerosol 6g Powder for Inhalation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ribavirin 6 g  
International non-proprietary name (INN): Ribavirin  
Chemical Name: 1-Beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide

3 PHARMACEUTICAL FORM

Powder for inhalation solution

4.1 Therapeutic indications

Virazole is recommended in the treatment of infants and children with severe respiratory syncytial virus (RSV) bronchiolitis.

Important: Ribavirin aerosol is more effective when instituted within the first 3 days of the treatment of bronchiolitis. Treatment early in the course of the disease may be necessary to achieve efficacy. In the absence of a positive proof of the RSV infection 24 hours after starting the therapy, it is recommended to continue the ribavirin therapy only after individual risk/benefit evaluation.

Treatment with Virazole must be accompanied by, and does not replace, standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Nebulised bronchodilators, when clinically indicated, should be administered with the Aiolos nebuliser turned off.

4.2 Posology and method of administration

Posology: Ribavirin aerosol is recommended for use in infants and children. In adults there are only limited data available and as such the safety and efficacy has not been established.

Aerosol administration or nebulisation should be carried out in an Aiolos nebuliser. Before use read the relevant Operator’s Manual for instructions.
The standard regimen is the use of 6g within 12 to 18 hours per day (solution of 20mg/ml) for at least 3 and no more than 7 days and is part of a total treatment programme.

Using the recommended drug concentration of 20 mg/ml, with the necessary flow for delivering 300 ml during 12 hours, the average aerosol concentration is 190 µg/l of air.

**Method of administration**
Please see point 6.6 for instructions on preparation of the aerosol solution.

The daily dose is prepared by dissolving 6 g of ribavirin in a minimum of 75 ml Water for Injection BP in the 100 ml vial. Shake well. Transfer dissolved drug and dilute to a total volume of 300 ml of Water for Injection BP to give a 20 mg/ml ribavirin solution. The solution must be clear and free of suspended particles.

The aerosol is delivered to an infant oxygen hood from the Aiolos nebuliser. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see Operator’s Manual). However, the volume of distribution and condensation area are larger in a tent and the efficacy of this method of administration has been evaluated only in a small number of patients.

*Application under assisted ventilation:* If the aerosol is used in children requiring assisted ventilation simultaneously, the patient and the respirator should be monitored carefully because a precipitation of ribavirin may narrow the respiratory route (filters, valves, tube). The filters and optionally the valves should be changed, e.g. within 2 – 4 h, each (see also section 4.4).

The Aiolis nebuliser should not be used to nebulise other drugs at the same time as ribavirin. Nebulised bronchodilators, when clinically indicated, should be administered with the Aiolos nebuliser turned off.

For prevention of occupational exposure see section 4.4

### 4.3 Contraindications

Hypersensitivity to the active substance ribavirin.

Ribavirin is contraindicated in females who are or may become pregnant and it should be noted that ribavirin can be detected in human blood even four weeks after oral administration has ceased.

### 4.4 Special warnings and precautions for use

Virazole should not be mixed with other medications in the same container. Treatment with bronchodilators in aerosol form should be administered with the Aiolos nebuliser turned off.
The use of ribavirin in children has been associated with a deterioration in pulmonary function. Also in patients with asthma, the use of ribavirin has been associated with a deterioration in pulmonary function.

Caution should be observed in treatment of patients with chronic obstructive pulmonary disease and asthma, since bronchospasm has been reported in the use of ribavirin.

Pulmonary function should be carefully monitored during the treatment. If a sudden deterioration of pulmonary function is observed, treatment should be stopped and reinstituted only with extreme caution and permanent monitoring.

Treatment with Virazole via aerosol in assisted ventilation should only take place under careful simultaneous monitoring of the patient and device since there is a risk of precipitation of the substance in the respirator unit. It is essential to control every hour, the possible precipitation and excessive condensation in the tubing. Likewise filters and valves should be routinely changed for example every 2 – 4 hours.

Directions for use during assisted ventilation are given in the Aiolos manual, which should be read carefully before such administration.

Haemoglobin or haematocrit should be monitored since haemolytic anaemia was reported in patients receiving oral ribavirin.

**Occupational exposure**

Nebulised Virazole may potentially escape into the hospital environment during therapy. Care should be exercised, particularly in healthcare workers with pre-existing reactive airways diseases.

Several methods have been employed to lower environmental exposure during Virazole use. The most practical of these is to turn off the Aiolos Nebuliser for 5 to 10 minutes prior to prolonged contact.

Ribavirin has been shown to be teratogenic in rabbits and rodents but not in baboons. However, no reports of teratogenicity in the offspring of mothers who were exposed to Virazole aerosol during pregnancy have been confirmed, and the teratogenic risk of Virazole to humans is unknown. Also a mutagenic effect cannot be excluded. As a precaution, women who are pregnant or trying to become pregnant and sexually active men should avoid exposure to the Virazole aerosol.

The container of this medicinal product contains latex rubber, which may cause severe allergic reactions.

### 4.5 Interactions with other medicinal products and other forms of interaction
4.6 Fertility, pregnancy and lactation

Pregnancy:
There are limited data from the use of Ribavirin in pregnant women (5 cases of measles-pneumonia and 1 case of influenza-pneumonia). Four pregnancies were completed and resulted in the birth of healthy children. A further 7 cases are known in which nurses administered Virazole dry substance during pregnancy (6) or just before conception (1). In 6 cases, healthy children were born. In one case, a chromosomal translocation was reported with mild developmental delay. Oral Ribavirin has been found to be teratogenic in rodents and rabbits, but was not teratogenic in baboons (see section 5.3)

Ribavirin is contraindicated in females who are or might become pregnant. Ribavirin can be detected in human blood four weeks after administration has ceased. Ribavirin therapy must not be started until a report of a negative pregnancy test has been obtained immediately before initiation of therapy. Routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within six months from stopping treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the conceptus.

Ribavirin accumulates intracellularly and is cleared from the body very slowly. Since a mutagenic effect also cannot be excluded, women of childbearing potential and sexually active men or their female partners of childbearing potential must use effective contraception during treatment and for 6 months thereafter. Monthly pregnancy tests should also be conducted as above.

Men whose partners are pregnant must be instructed to use a condom to minimise delivery of ribavirin to the partner.

Breast feeding
There are no data on the effects of ribavirin during human lactation and it is not known whether ribavirin passes into human milk. Ribavirin should not be used during breast feeding. Breast feeding should be avoided for 6 months after the cessation of dosing.

Fertility
There is no information on fertility in humans. Animal studies have shown testicular effects (see section 5.3) but fertility was unaffected.
4.7 Effects on ability to drive and use machines

Virazole has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse drug reactions are stated in the table below using the following convention:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from available data)

Blood and lymphatic system disorders:
- Rare: Haemolysis, anaemia, haemolytic anaemia, reticulocytosis

Immune system disorders:
- Frequency not known: The rubber closure contains natural rubber. Natural rubber may cause hypersensitivity or severe allergic reactions.

Nervous system disorders:
- Rare: Headache

Eye disorders:
- Rare: Conjunctivitis

Cardiac disorders:
- Rare: Cardiac arrest
- Frequency not known: Bradycardia, tachycardia

Vascular disorders:
- Frequency not known: Hypertension, hypotension

Respiratory, thoracic and mediastinal disorders:
- Rare: Bacterial pneumonia, pneumothorax, laryngitis, pharyngitis
- Very rare: Dyspnoea, cough, hypo- and hyperventilation, apnoea
- Frequency not known: Bronchospasm

Gastrointestinal disorders:
- Frequency not known: Nausea, vomiting, abdominal pain

Hepatobiliary disorders:
- Uncommon: Hepatic function abnormal

Skin and subcutaneous tissue disorders:
- Frequency not known: Rash, skin irritation, pruritus, exanthema, erythema

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal
product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

**Symptoms:**
If Virazole lyophilisate for aerosol is improperly used (i.e. as an injection) or inhaled over too short a period, there may be seizures, hypoventilation or disturbances of cardiac function.

**Management:**
In case of overdose, ribavirin therapy should be discontinued immediately. No specific antidote is known so treatment should be symptomatic.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct acting antivirals.

ATC code: J05AB04

Ribavirin has anti-viral inhibitory activity in vitro against respiratory syncytial virus, influenzae virus and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus in experimentally infected cotton rats.

The inhibitory activity of ribavirin on RSV in cell cultures is selective. The mechanism of action is unknown, but there is evidence that ribavirin interferes with protein translation by mRNA of several other RNA viruses, possibly the result of interference with formation of the 5' cap structure of mRNA.

5.2 Pharmacokinetic properties

**Absorption:**
After nasal and oral inhalation, systemic absorption occurs through the respiratory tract. The amount of drug which passes into the respiratory tract is proportional to concentration and duration of inhalation therapy. Maximum plasma concentrations are usually measured at the end of the inhalation period and they are also dependent on the duration of inhalation.

The bioavailability of inhaled ribavirin is unknown and may depend on the mode of aerosol delivery. At a daily inhalation of 20h for 5 days, the mean plasma concentration was 1.66 µg/ml. The measured concentrations in the respiratory secretions are substantially higher than in plasma, where a concentration is not reached effective against respiratory syncytial virus.

**Distribution:**
After nasal and oral inhalation, the highest ribavirin concentrations are found in the respiratory tract and in erythrocytes. Ribavirin is retained in the body and accumulates intracellularly especially in erythrocytes. In humans, after a single dose ribavirin reaches a plateau in erythrocytes after about 4 days that declines slowly with a half-life of 40 days. Ribavirin binds only slightly to plasma proteins. Ribavirin penetrates the blood brain barrier. At high ribavirin doses, the CSF may
reach concentrations comparable to plasma levels. It is not known whether ribavirin crosses the placental barrier and whether it is excreted into breast milk.

**Metabolism:**
Probably in the liver, ribavirin is largely metabolised to 1,2,4-triazole-3-carboxamide, with a mode of action similar to ribavirin. The substance is also converted to 1,2,4-triazole-3-carboxylic acid. Other active metabolites necessary for efficacy are derived from intracellular phosphorylation.

**Elimination:**
After nasal and oral inhalation in a limited number of paediatric patients, the plasma half-life and the half-life of ribavirin in the respiratory tract was 9.5 hours and 1.4 to 2.5 hours on average, respectively. An essentially longer terminal plasma half-life of 24 hours has to be taken into account. Ribavirin may persist in nonplasma compartments for as long as 6 months.

In healthy adults with normal renal function about 53% of a single oral dose was recovered in urine within 72-80 hours. After 1.5 – 2 hours, the excretion into the urinary fraction was 37% as ribavirin, 30% as 1,2,4-triazole-3-carboxamide and 1,2,4-triazole-3-carboxylic acid each. After 24 hours these values accounted for 17%, 50% and 22% respectively. About 15% of a single dose was excreted with 72 hours in the faeces.

5.3 **Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology. Repeat-dose studies in mice showed sperm abnormalities and testicular toxicity that recovered nearly completely after two spermatogenic cycles. In rats, decreased weights of the seminal vesicle and prostate were found but there were no effects on fertility. These effects occurred at doses below the clinical dose.

Ribavirin was found to be teratogenic and / or embryotoxic in mice, rats, rabbits and hamsters at doses below the clinical dose. Malformations of the skull, palate, eyes, jaw, limbs, skeleton and gastro-intestinal tract were noted. The incidence and severity of teratogenic effects increased with increasing dose. A study of primates (baboons) given up to 120 mg/kg/day orally between days 20 and 29 of gestation has found no evidence of malformations, but is not extensive enough to exclude such a risk with any certainty.

In vivo and in vitro studies revealed some evidence of mutagenic effects in mammalian cells. Although in similar assays there were also negative results, the possibility cannot be ruled out that ribavirin, like other analogues of DNA building blocks, might have a mutagenic effect.

In rats exposed to ribavirin with food, an increased incidence of benign tumours occurred. Since ribavirin induces malignant transformation in mammalian cell cultures, a carcinogenic potential cannot be ruled out until further information is available.
6.1 List of excipients:

None

6.2 Incompatibilities

This medicinal product must neither be mixed nor nebulised at the same time with other medicinal products.

6.3 Shelf life

5 years

Virazole should be reconstituted in Water for Injection BP and prepared immediately prior to use. The preparation must not be stored.

Virazole must not be used if visible particles in the aerosol solution, cloudy solution or discoloration are observed.

6.4 Special precautions for storage

Store in a dry place. Store below 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

100ml Type 1 glass serum bottle with butyl rubber closure and aluminium seal with tear-off septum. Each bottle contains 6g ribavirin as a lyophilised white cake. Virazole is packaged in cartons of three bottles.
6.6 Special precautions for disposal

By aseptic technique dissolve the powder in 50 to 100 ml Water for Injection BP in the 100 ml vial. The solution should be adequately mixed to ensure complete dissolution. Shake well. It is not recommended that this solution is heated during dissolution.

When using the Aiolos nebuliser, transfer the solution into an infusion bag and dilute to a final volume of 300 ml with Water for Injection BP. The final concentration should be 20 mg/ml.

The Water for Injection BP used to make up the Virazole solution should not have any antimicrobial agents or any other substance added and all solutions should be inspected for particulate matter and discolouration prior to administration.

See guidelines for avoiding unwanted exposure to Virazole aerosol under 4.4 Special warnings and precautions for use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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