APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

AURO-RIBAVIRIN TABLETS 200 mg (Tablet)

COMPOSITION:

Each film-coated tablet contains 200 mg Ribavirin.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

AURO-RIBAVIRIN TABLETS 200 mg (ribavirin) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication (see **WARNINGS**). The primary clinical toxicity of ribavirin is haemolytic anaemia. The anaemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin (see **WARNINGS, SIDE EFFECTS**, and **DOSAGE AND DIRECTIONS FOR USE**).

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Ribavirin therapy is contra-indicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period (see **CONTRA-INDICATIONS**, **WARNINGS**, and **SPECIAL PRECAUTIONS**).

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Ribavirin is a purine nucleoside analogue with a modified base and D-ribose sugar. Ribavirin inhibits the replication of a wide range of RNA and DNA viruses. The antiviral mechanism of ribavirin is not fully defined but relates to alteration of cellular nucleotide pools and inhibition of viral messenger RNA synthesis.

Pharmacokinetics:

Ribavirin is actively taken up by gastrointestinal nucleoside transporters located in the proximal small bowel, and oral bioavailability averages approximately 50 %. Extensive accumulation occurs in plasma, and steady state is reached by about 4 weeks. Food increases plasma levels substantially, so ingestion with food may be prudent. Following single or multiple oral doses of 600 mg and 1200 mg, peak plasma concentrations average 0,8 µg/ml and 3,7 µg/ml, respectively.

Ribavirin has shown high inter- and intra subject pharmacokinetic variation.

PHARMACOKINETICS IN SPECIAL POPULATIONS:

Patients with renal impairment:

Single-dose ribavirin pharmacokinetics were altered (increased AUC_{tf} and C_{max}) in patients with renal dysfunction compared with control subjects whose creatinine clearance was greater than 90 ml/minute. The clearance of ribavirin is substantially reduced in patients with renal dysfunction, serum creatinine > 2 mg/dl or creatinine clearance < 50 ml/min. Ribavirin has been used in dialysis patients with hepatitis C infection at substantially reduced doses of 100 mg to 300 mg daily.

The use of ribavirin in patients with severe renal impairment requires close monitoring of ribavirin plasma concentrations and haemoglobin. Plasma concentrations of ribavirin are essentially unchanged by haemodialysis.

Patients with hepatic dysfunction:

Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction are similar to those of normal controls.

Elderly patients (> 65 years of age):

Specific pharmacokinetic evaluations for elderly subjects have not been performed. However, in a population pharmacokinetic study, age was not a key factor in the kinetics of ribavirin; renal function is the determining factor.

Patients under the age of 18 years:

AURO-RIBAVIRIN TABLETS 200 mg has not been evaluated in patients under the age of 18 years.

INDICATIONS:

AURO-RIBAVIRIN TABLETS 200 mg, in combination with peginterferons, is indicated for the treatment of chronic hepatitis C. **AURO-RIBAVIRIN TABLETS 200 mg** must not be used alone.

AURO-RIBAVIRIN TABLETS 200 mg is only indicated for the treatment of adult patients over the age of 18 years with chronic hepatitis C, who have elevated transaminases who are positive for serum HCV RNA and who have compensated liver disease.

CONTRA-INDICATIONS:

Please refer to the package insert of peginterferons alfa for contra-indications related to these products.

In addition, **AURO-RIBAVIRIN TABLETS 200 mg** is also contra-indicated in:

- Patients with hypersensitivity to the active substance or to any of the excipients
- Women who are pregnant or who intend to become pregnant
- Men whose female partners are pregnant
- Patients with haemoglobinopathies (e.g. thalassemia major or sickle-cell anaemia)
- Patients with autoimmune hepatitis
- Patients with moderate to severe hepatic impairment (Child-Pugh class B and C)
- Patients with moderate to severe renal impairment (C_{cr} < 50 ml/min)

WARNINGS:

Monotherapy: AURO-RIBAVIRIN TABLETS 200 mg must not be used alone as AURO-RIBAVIRIN TABLETS 200 mg monotherapy is not effective for the treatment of chronic hepatitis C.

General: AURO-RIBAVIRIN TABLETS 200 mg used in combination therapy should be administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of further therapy.

Pregnancy:

AURO-RIBAVIRIN TABLETS 200 mg must not be used in women who are pregnant or intend to become pregnant (see CONTRA-INDICATIONS). AURO-RIBAVIRIN TABLETS 200 mg may cause birth defects and/or death of the exposed foetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. AURO-RIBAVIRIN TABLETS 200 mg therapy must

not be started unless a report of a negative pregnancy test has been obtained prior to the planned initiation of therapy. Prior to initiation of treatment with AURO-RIBAVIRIN TABLETS 200 mg the physician must comprehensively inform the patient of the teratogenic risk of AURO-RIBAVIRIN TABLETS 200 mg, the necessity of effective and continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with AURO-RIBAVIRIN TABLETS 200 mg.

Anaemia:

The primary toxicity of AURO-RIBAVIRIN TABLETS 200 mg is haemolytic anaemia (haemoglobin <10 g/dl). Anaemia associated with AURO-RIBAVIRIN TABLETS 200 mg occurs approximately within 1 to 2 weeks of initiation or therapy. Because the initial drop in haemoglobin may be significant, it is advisable that haemoglobin or haematocrit be obtained pre-treatment and at week 2 and 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate. Although AURO-RIBAVIRIN TABLETS 200 mg has no direct cardiovascular effects, anaemia associated with AURO-RIBAVIRIN TABLETS 200 mg may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, AURO-RIBAVIRIN TABLETS 200 mg must be administered with caution to patients with pre-existing cardiac disease.

Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy should be stopped (see Table 3: AURO-RIBAVIRIN TABLETS 200 mg dosage modification guidelines). It is recommended that those patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment.

Hepatic decompensation:

In patients who develop evidence of hepatic decompensation during treatment, AURO-RIBAVIRIN TABLETS 200 mg should be discontinued. When the increase in ALT levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased bilirubin, therapy should be discontinued.

Renal function:

It is recommended that the renal function be evaluated in all patients prior to initiation of **AURO-RIBAVIRIN TABLETS 200 mg** therapy. Substantial increases in **AURO-RIBAVIRIN TABLETS 200 mg** plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine > 2 mg/dl or

with creatinine clearance < 50 ml/minute. In these patients, **AURO-RIBAVIRIN TABLETS 200 mg** is contra-indicated.

Laboratory tests:

Standard haematologic tests and blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid) must be conducted in all patients prior to initiating therapy.

After initiation of **AURO-RIBAVIRIN TABLETS 200 mg** therapy, laboratory evaluations should be performed at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. Acceptable baseline values that may be considered as a guideline prior to initiation of **AURO-RIBAVIRIN TABLETS 200 mg** in combination with peginterferons alfa are:

Haemoglobin: ≥ 12 g/dl (females); ≥ 13 g/dl (males)

Platelets: ≥ 90 000/mm^3

Neutrophil Count: ≥ 1 500/mm^3

INTERACTIONS:

Interaction studies have been conducted with ribavirin, such as in **AURO-RIBAVIRIN TABLETS 200 mg** in combination with peginterferons alfa and antacids. **AURO-RIBAVIRIN TABLETS 200 mg** concentrations are similar when given alone or concomitantly with peginterferons alfa. Any potential for interactions may persist for up to 2 months (5 half-lives for **AURO-RIBAVIRIN TABLETS 200 mg**) after cessation of **AURO-RIBAVIRIN TABLETS 200 mg** therapy due to the long half-life.

Cytochrome P450 enzymes:

Results of in-vitro studies with ribavirin such as in **AURO-RIBAVIRIN TABLETS 200 mg**, using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme-mediated metabolism of **AURO-RIBAVIRIN TABLETS 200 mg**. **AURO-RIBAVIRIN TABLETS 200 mg** does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that **AURO-RIBAVIRIN TABLETS 200 mg** induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions.

Antacid:

The bioavailability of **AURO-RIBAVIRIN 600 mg** is decreased by co-administration with an antacid containing magnesium, aluminium and methicone; AUC_{tf} decreases 14 %. It is possible that the decreased bioavailability

in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.

Nucleoside analogues:

Ribavirin was shown in-vitro to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these in-vitro findings raise the possibility that concurrent use of ribavirin with either zidovudine or stavudine might lead to increased HIV plasma viremia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with **AURO-RIBAVIRIN TABLETS 200 mg** concurrently with either of these two agents. If HIV RNA levels increase, the use of **AURO-RIBAVIRIN TABLETS 200 mg** concomitantly with reverse transcriptase inhibitors must be reviewed.

PREGNANCY AND LACTATION:

Pregnancy: AURO-RIBAVIRIN TABLETS 200 mg must not be used by women who are pregnant or by men whose female partners are pregnant (see **CONTRA-INDICATIONS** and **WARNINGS**).

Evaluation of experimental animal studies showed reproductive toxicity. Significant teratogenic and/or embryocidal potential have been demonstrated for **AURO-RIBAVIRIN TABLETS 200 mg** in all animal species in which adequate studies have been conducted. Extreme care must be taken to avoid pregnancy in female patients.

AURO-RIBAVIRIN TABLETS 200 mg therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation or therapy.

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential and their partners must use 2 forms of effective contraception simultaneously, during treatment and for 6 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within 6 months from stopping treatment the patient must be advised of the significant teratogenic risk of **AURO-RIBAVIRIN TABLETS 200 mg** to the foetus.

Male patients and their female partners:

Extreme care must be taken to avoid pregnancy in partners of male patients taking **AURO-RIBAVIRIN TABLETS 200 mg**. **AURO-RIBAVIRIN TABLETS 200 mg** accumulates intra-cellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the **AURO-RIBAVIRIN TABLETS 200 mg** that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Therefore, men must be instructed to use a condom to minimize delivery of **AURO-RIBAVIRIN TABLETS 200 mg** to their partners. Male patients and their female

partners of childbearing age must be counselled to use 2 forms of effective contraception during treatment with **AURO-RIBAVIRIN TABLETS 200 mg** and for 6 months after treatment has been concluded.

Lactation:

It is not known whether **AURO-RIBAVIRIN TABLETS 200 mg** is excreted in human milk. Because of the potential for adverse reactions in nursing infants, a decision should be made either to discontinue nursing or not to initiate therapy.

If an acute hypersensitivity reaction (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, **AURO-RIBAVIRIN TABLETS 200 mg** must be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

DOSAGE AND DIRECTIONS FOR USE:

The tablets should not be broken or crushed. Since **AURO-RIBAVIRIN TABLETS 200 mg** is considered a potential teratogen, caution should be observed in handling broken tablets. Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.

Standard dosage: The daily dose of **AURO-RIBAVIRIN TABLETS 200 mg** is to be administered orally in two divided doses, morning and evening, with food (see Table 1).

Table 1: AURO-RIBAVIRIN TABLETS 200 mg Dosing Recommendations in combination with peginterferons

Genotype	**Daily AURO-RIBAVIRIN TABLETS 200 mg Dose**	**Duration of treatment**	**Number of 200 mg tablets**
Genotype 1, 4*	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	48 weeks 48 weeks	5 (2 morning; 3 evening) 6 (3 morning; 3 evening)
Genotype 2, 3	800 mg (regardless of weight)	24 weeks	4 (2 morning; 2 evening)

* sustained virologic response is highest in patients treated for 48 weeks with 1000 mg or 1200 mg of **AURO-RIBAVIRIN TABLETS 200 mg.**

Special dosage instructions:

Dosage modification for adverse reactions: If severe adverse reactions or laboratory abnormalities develop during therapy with **AURO-RIBAVIRIN TABLETS 200 mg**, the dosages of **AURO-RIBAVIRIN TABLETS 200 mg** should be modified until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Table 2). Because of the recognized haemolysis associated with **AURO-RIBAVIRIN TABLETS 200 mg** therapy, separate guidelines are provided for patients with a history of cardiovascular disease.

If intolerance persists after dose adjustment, discontinuation of **AURO-RIBAVIRIN TABLETS 200 mg** may be necessary.

Table 2: AURO-RIBAVIRIN TABLETS 200 mg Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia

Laboratory Values	**Reduce AURO-RIBAVIRIN TABLETS 200 mg dose to 600 mg/day* if:**	**Discontinue AURO-RIBAVIRIN TABLETS 200 mg if**:**
Haemoglobin in patients with no cardiac disease	< 10 g/dl	< 8,5 g/dl
Haemoglobin in patients with history of stable cardiac disease	> 2 g/dl decrease in haemoglobin during any 4 week period during treatment	< 12 g/dl despite 4 weeks at reduced dose

* One 200 mg tablet in the morning and two 200 mg tablets in the evening.

** If the abnormality is reversed, **AURO-RIBAVIRIN TABLETS 200 mg** may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to original dosing is not recommended.

Dosage in special populations:

Use in renal impairment:

The pharmacokinetics of **AURO-RIBAVIRIN TABLETS 200 mg** are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of **AURO-RIBAVIRIN TABLETS 200 mg**, preferably by estimating the patient's creatinine clearance. Substantial increases in plasma concentrations are seen at the

recommended dosing regimen in patients with serum creatinine > 2 mg/dl or with creatinine clearance < 50 ml/minute. In these patients**, AURO-RIBAVIRIN TABLETS 200 mg** is contra-indicated (see **WARNINGS**).

Use in hepatic impairment:

No pharmacokinetic interaction appears between **AURO-RIBAVIRIN TABLETS 200 mg** and hepatic function. Therefore, no dose adjustment of **AURO-RIBAVIRIN TABLETS 200 mg** is required in patients with mild hepatic impairment (see **CONTRA-INDICATIONS**).

Use in the elderly (> 65 years of age):

There does not appear to be a significant age-related effect on the pharmacokinetics of **AURO-RIBAVIRIN TABLETS 200 mg**. However, as in younger patients, renal function must be determined prior to administration of **AURO-RIBAVIRIN TABLETS 200 mg**.

Use in patients under the age of 18 years:

Safety and efficacy of **AURO-RIBAVIRIN TABLETS 200 mg** in combination with peginterferons alfa in these patients have not been evaluated. Treatment with **AURO-RIBAVIRIN TABLETS 200 mg** is not recommended for use in children and adolescents under the age of 18.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

Blood and the lymphatic system disorders:

Frequent: Anaemia, lymphadenopathy.

Endocrine disorders:

Frequent: Hyperthyroidism, hypothyroidism.

Metabolism and nutritional disorders:

Frequent: Anorexia, weight decrease.

Psychiatric disorders:

Frequent: Depression, irritability, concentration impairment, taste disturbance, mood alteration, insomnia, dizziness, memory impairment, paraesthesia, hypaesthesia, tremor, emotional disorders, nervousness, aggression, libido decrease, impotence, anxiety.

Less frequent: Attempted suicide, substance overdose, vertigo, coma.

Eye disorders:

Frequent: Blurred vision, xerophthalmia, eye inflammation, eye pain.

Less frequent: Corneal ulcer.

Cardiac disorders:

Frequent: Palpitations.

Less frequent: Endocarditis, arrhythmia, atrial fibrillation, pericarditis, angina pectoris.

Vascular disorders:

Less frequent: Cerebral haemorrhage.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, sinus congestion, cough, chest tightness, upper respiratory tract infection, sore throat, rhinitis, nasopharyngitis, pulmonary congestion, dyspnoea exertional, epistaxis.

Less frequent: Lower respiratory tract infection, interstitial pneumonitis, pulmonary embolism.

Gastrointestinal disorders:

Frequent: Abdominal pain, dyspepsia, vomiting, nausea, diarrhoea, gastritis, flatulence, dry mouth, mouth ulceration, gingival bleeding, gingivitis, cheilitis, constipation.

Less frequent: Peptic ulcer, gastrointestinal bleeding.

Hepato-biliary disorders:

Less frequent: Hepatic dysfunction, fatty liver, cholangitis, malignant hepatic neoplasm, reversible pancreatic reaction, auto immune phenomena (e.g. idiopathic thrombocytopenic purpura).

Skin and subcutaneous tissue disorders:

Frequent: Pruritus, alopecia, dermatitis, dry skin, skin disorder, rash, eczema, psoriasis, urticaria, photosensitivity reaction, increased sweating, night sweats.

Less frequent: Skin infection.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia, muscle cramps, musculoskeletal pain, bone pain, back pain, neck pain, muscle weakness.

Less frequent: Myositis.

General disorders and administration site conditions:

Frequent: Asthenia, rigors, chest pain, fatigue, headache, pyrexia, pain, injection site reaction, influenza-like illness, malaise, lethargy, shivering, hot flushes, weakness, weight decrease.

Less frequent: Otitis externa, peripheral neuropathy.

Investigations:

Most cases of anaemia, leucopenia and thrombocytopenia were mild. Please refer to **WARNINGS**. An increase in uric acid and indirect bilirubin values associated with haemolysis were observed in some patients treated with **AURO-RIBAVIRIN TABLETS 200 mg** used in combination with peginterferons alfa and values returned to baseline levels within 4 weeks after the end of therapy.

Special precautions:

If severe side effects or laboratory abnormalities develop during therapy with **AURO-RIBAVIRIN TABLETS 200 mg**, modify the dosage until the severe side effects abate. If intolerance persists after dose adjustment, discontinuation of **AURO-RIBAVIRIN TABLETS 200 mg** may be necessary (see **DOSAGE AND DIRECTIONS FOR USE** and **Special dosage instructions**).

Use of machinery:

AURO-RIBAVIRIN TABLETS 200 mg alone has no or negligible influence on the ability to drive or operate machinery. Patients who develop fatigue, somnolence, or confusion during treatment must be cautioned to avoid driving or operating machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No cases of overdose have been reported with **AURO-RIBAVIRIN TABLETS 200 mg**. Treatment should be supportive and symptomatic.

IDENTIFICATION:

Light pink coloured, capsule shaped, film coated tablets, with 'F' debossed on one side and '10' on the other side.

PRESENTATION:

1) Tablets are packed in a 40 ml white opaque HDPE container with a 33 mm neck finish and 33 mm – 400 stock ribbed closure with induction sealing wad. Each container contains 28 tablets.

   Pack size: 28's – One white opaque HDPE container of 28 tablets.

2) Tablets are packed in a 250 ml white opaque HDPE container with a 53 mm neck finish and 53 mm – 400 stock ribbed closure with induction sealing wad. Each container contains 500 tablets.

   Pack size: 500's – One white opaque HDPE container of 500 tablets.

STORAGE INSTRUCTIONS:

Store below 25 °C. Keep container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

43/20.2.8/0499

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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