interferon alfa 2b (Viraferon® and Intron A*®) 18 million IU, solution for injection, multidose pen in combination with ribavirin (Rebetol®) capsules 200 mg No. (258/06)

Schering Plough

5 May 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Interferon alfa 2b (Viraferon® and Intron A®) in combination with ribavirin (Rebetol) is accepted for use within NHS Scotland for the treatment of children and adolescents 3 years of age and older, who have chronic hepatitis C, not previously treated, without liver decompensation and who are positive for serum HCV-RNA.

The combination is effective in eliminating hepatitis C virus in children and adolescents. The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load. The expected benefit of treatment should be weighted against the safety findings observed for paediatric subjects in the clinical trials.
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Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Interferon alfa 2b, 18 MIU injection (Viraferon® or Intron A®) in combination with ribavirin 200 mg capsules (Rebetol®)

Indication

Treatment of children and adolescents 3 years of age or over, who have chronic hepatitis C, not previously treated, without liver decompensation and who are positive for serum HCV-RNA.

The Summary of Product Characteristics (SPC) for interferon alfa 2b adds, "The decision to treat should be made on a case by case basis, taking into account any evidence of disease progression such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load."

Dosing information

Interferon alfa 2b 3MIU/m^2 subcutaneously three times a week (every other day) in combination with ribavirin at a dose based on body weight.

The recommended duration for patients with genotype 2 or 3 is 24 weeks. For patients with genotype 1, the recommended duration is one year. However therapy should be discontinued in those who fail to achieve a viral response (defined as absence of detectable HCV-RNA) at week 12.

UK launch date

Licensed January 2005

Comparator medications

There are no comparator medications licensed for use in this age group.

Cost of treatment

Product	Regimen	Cost per 24 weeks (alternate days)
Interferon alfa 2b (Viraferon®) multidose pen	4.5 MIU sub-cutaneously (sc) 3 times a week (every other day)	£1898
Interferon alfa 2b (Intron A®) multidose pen	4.5 MIU sc 3 times a week (every other day)	£1633
Ribavirin (Rebetol®) capsules	600 mg daily (200 mg capsules, 1 morning, 2 evening)	£1654

Doses are shown for general comparison and do not imply therapeutic equivalence

Acquisition costs are based on 24 weeks' therapy for a patient with a body surface area of 1.5 m^2 (e.g. a male with a height of about 60 inches and weight of 47-49 kg). The total cost is the cost of interferon plus ribavirin.

For patients weighing <47 kg the dosage recommendations in the Summary of Product Characteristics (SPC) for Rebetol® capsules refer to the SPC for the oral solution. As the

oral solution is currently unavailable, this will create difficulties in dosing patients below this weight and those with difficulty in swallowing capsules.

Summary of evidence on comparative efficacy

Interferon alfa 2b is an immunomodulator the actions of which include inhibition of viral replication in virus-infected cells. Ribavirin is an antiviral that had no effect on eliminating hepatitis C in clinical trials but which enhances the activity of interferons.

In an open-label dose-finding trial, 61 patients aged 5-16 years with chronic hepatitis C and no evidence of cirrhosis were randomised to ribavirin 8, 12 or 15 mg/kg/day in combination with interferon alfa 2b 3 MIU/m^2 three times per week. Patients were either interferon naïve or had relapsed on previous interferon, but non-responders were not eligible. Based on comparative safety and viral response data in this cohort the optimal dose of ribavirin for further study in combination with interferon alfa 2b 3 MIU/m^2 was identified as 15mg/kg/day. This regimen was used in a second cohort and in another open label non-comparative study involving treatment-naïve patients aged 3-16 years.

For both cohorts in the first study the primary objectives were investigation of safety and pharmacokinetics of combination therapy but sustained viral response (SVR) was measured as undetectable HCV-RNA (<100 copies/ml) at the end of 24-weeks' follow up after a 48-week treatment period. This was the primary end-point for the third study. In all arms of these studies, patients who did not achieve a pre-defined viral response at 24 weeks were withdrawn and defined as non-responders.

The results for patients receiving interferon alfa 2b 3 MIU/m^2 three times per week and ribavirin at a dose of 15mg/kg/day were pooled from a sub-group of the dose-finding study and the other two study populations in an analysis with SVR as the primary end-point. Across all three studies, 46% (54/118) of patients achieved SVR. The likelihood of SVR was substantially higher for patients of genotype 2 or 3 than for those of genotype 1 (84% [21/25] versus 36% [33/92] p<0.01): One patient discontinued because of a lack of viral response at 12-14 weeks and 38/118 were classified as treatment failure, with discontinuation for lack of response between weeks 24 and 28.

In an open-label comparative study 76 adults and 37 adolescents were randomised to interferon alfa 2b 3 MIU/m^2 three times per week with or without ribavirin 1000 mg/day for 48 weeks and the rate of achieving SVR (as defined above) among the adolescents was 59% (10/17) for patients on combination therapy. This was higher than the rate for adults (15% [6/39] p=0.001).

Stepwise logistic regression analyses on the entire patient population in this study demonstrated that being under 18 years of age increased the odds of SVR 11-fold (95% confidence interval [CI]: 2.7, 42), while treatment with interferon-alpha and ribavirin rather than interferon-alpha alone increased the odds 9.8-fold (95% CI: 2.3, 42). The proportion of adolescents receiving monotherapy who achieved SVR was not stated. However, the overall rate of achieving SVR was 29% (16/56) with combination therapy and 7.0% (4/57) for monotherapy.

The company submission included an analysis of five studies reporting the proportion of patients receiving combination therapy with interferon alfa 2b 3 MIU/m^2 three times per week and ribavirin 15mg/kg/day, sub-divided by genotype, who achieved SVR. Almost all patients received treatment for 48-52 weeks, and follow-up varied from 24 weeks to one year. The number of patients achieving SVR with combination therapy in five studies, sub-divided by

hepatitis C genotype were for all patients 126/247 (51%:95% CI 45%,57%; genotype 1 53/131 (40%: 95% CI 32%, 49%) and genotype 2/3 33/37 (89%: 95% CI 79%, 99%).

Summary of evidence on comparative safety

In a pooled analysis of 118 trial patients with a median age of 11 years receiving interferon alfa 2b 3 MIU/m^2 three times per week and 15mg/kg/day ribavirin, all patients reported at least one adverse event. More than 80% of events were mild to moderate in severity, while severe adverse events occurred in 23 patients (19%). The rate of linear growth decreased by 9 percentiles during the 1-year course of treatment and this was partially compensated with a 2-percentile increase between end of treatment and six months' follow-up. Based on interim data from a long-term follow-up study, 12/84 children (14%) had a >15 percentile decrease and 5/84 (6%) had a >30 percentile decrease despite being off treatment for one year. There are no data on long-term effects on growth and development and on sexual maturation. There was one attempted suicide.

Children and adolescents require monitoring of thyroid function before and during treatment because abnormalities in thyroid stimulating hormone levels have been observed during treatment.

When the analysis was expanded to include other studies in the company's submission, 12/249 (4.8%) discontinued because of adverse events and 51/219 (23%) required dose modification.

Summary of clinical effectiveness issues

Ribavirin is not currently available as an oral solution, and dosage recommendations for the capsules do not cover patients <47 kg. This will create problems in prescribing for lighter patients and those who have difficulty swallowing capsules.

Summary of comparative health economic evidence

The manufacturer provided a cost utility analysis comparing interferon alpha 2b and ribavirin to (1) 'no treatment/ best supportive care', (2) delayed treatment with pegylated interferon alpha 2b and ribavirin when the patient reached the age of 18 or (3) immediate treatment with pegylated interferon alpha 2b and ribavirin which is currently unlicensed for this age group. A Markov model was used with transition probabilities derived from the key interferon alpha 2b and ribavirin trials in children and from a systematic review of the literature for other values. The model looked at the cost-effectiveness of the different treatments over a range of time horizons (one to sixty years) but the baseline results were presented using a lifetime perspective. Utility values were taken from the adult Mild Hepatitis C study. The analysis did make an allowance for the disutility associated with the process of treatment. Drug resource use for interferon alpha 2b and ribavirin was estimated from actual usage within the clinical trials and other resource use associated with the various disease states within the model (e.g. cirrhosis, liver transplant, severe hepatitis C) were estimated from the Mild Hepatitis C study. For children < 47kg, the model used a provisional price of ribavirin solution which was equal to the per milligram cost of ribavirin capsules.

The results indicated a cost per QALY of £490 for interferon alpha 2b and ribavirin compared to the no treatment option. Compared to delayed treatment in adulthood, interferon alpha 2b and ribavirin was both cheaper and more effective. The use of unlicensed pegylated

interferon alpha 2b and ribavirin was associated with an incremental cost per QALY (ICER) of £1200. When the comparisons were conducted for patients of different genotypes, the results showed that treatment was more cost-effective in patients of genotype 2/3 than in genotypes 1,4,5 and 6. Extensive sensitivity analysis was undertaken which showed that the cost-effectiveness of interferon alpha 2b and ribavirin compared to no treatment or delayed treatment was largely robust. The ICER for immediate pegylated combination treatment (i.e. using unlicensed pegylated interferon) also appeared to be a generally cost-effective treatment alternative to interferon alpha 2b and ribavirin.

The analysis was well conducted and demonstrated that interferon alpha 2b and ribavirin was a cost-effective treatment option compared to a strategy of no treatment.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer undertook a budget impact analysis considering a range of scenarios regarding treatment uptake in the patient population. If all children and adolescents with hepatitis C were treated (110 patients in year one and 30 per annum thereafter) the drug budget impact compared to 'no current treatment' was £510,000 in the first year and then £140,000 in each subsequent year. At a level of uptake of 17% of the patient population (based on previous studies of liver biopsy findings in children and adolescents) the drug budget impact was estimated as £86,600 in the first year and £22,000 in subsequent years. Only 5% of adult patients with chronic hepatitis C receive active treatment and therefore if only 5% of the child and adolescent population also received treatment then the drug budget impact was £25,500 in the first year and £6,700 per annum thereafter. In addition to the drug budget impact there would also be costs incurred for testing and monitoring of patients on drug therapy. The calculations also used a provisional cost for ribavirin solution, as in the economic analysis, which could be subject to change.

Guidelines and protocols

Current NICE guidance, *Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C*, advises combination therapy with peginterferon alfa (in preference to interferon alfa) and ribavirin within their licensed indications for adults with moderate to severe chronic hepatitis C. These guidelines (updated in 2004) state that there is insufficient evidence to recommend combination therapy with peginterferon alfa or interferon alfa in patients aged <18 years, but the guidance pre-dates licensing for children and adolescents.

Additional information

In May 2002, SMC advised that pegylated interferon alfa-2b (ViraferonPeg®) is an appropriate treatment for the management of adult patients with chronic hepatitis C under the overall supervision of specialists experienced in the management of this disorder. This treatment involves a once weekly injection that reduces inconvenience to patients whilst increasing the response rate to both pegylated interferon alfa-2b alone or in combination with ribavirin.

In September 2002, SMC recommended pegylated interferon alfa-2a (Pegasys®) for restricted use within NHS Scotland. Pegylated interferon alfa-2a is an appropriate treatment for the treatment of adult patients with chronic hepatitis C under the overall supervision of specialists experienced in the management of this disorder. This treatment involves a weekly injection from a pre-filled syringe that reduces inconvenience to patients whilst increasing the response rate over interferon alfa-2a alone or in combination with ribavirin.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 April 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission.

National Institute for Clinical Excellence, Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C, in Technology Appraisal Guidance No. 75; January 2004: London.

Gonzalez-Peralta RP, Kelly DA, Haber Bet al. Interferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C in children: Efficacy, safety, and pharmacokinetics. Hepatology, 2005; 42: 1010-8.

Fried MW, Peter J, Hoots Ket al. Hepatitis C in adults and adolescents with hemophilia: a randomized, controlled trial of interferon alfa-2b and ribavirin. Hepatology, 2002; 36: 967-72.

Gonzalez-Peralta RP, Haber B, Jonas M, Albrecht J and et al, Interferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C in children. Hepatology, 2002; 36:591A.