February 26, 2001

Dear Primary Hepatitis C Clinician:

The Food and Drug Administration (FDA) approved a new antiviral on January 22, 2001 for the treatment of hepatitis C called as peginterferon alfa-2b (PEG-Intron™). This compound is currently commercially available for prescribing for appropriate clinical indications. PEG-Intron is an agent comprised of standard interferon alfa-2b (INTRON A™) attached to multiple linear 12 kilodalton polyethylene glycol molecules. While the pharmacologic activity of PEG-Intron is similar to INTRON-A, there are significant differences in the pharmacokinetic parameters of the two molecules. After single subcutaneous injections, PEG-Intron is absorbed more slowly than INTRON A. Clearance of PEG-Intron is reduced by 7-fold and half-life increased by 5-fold when compared to INTRON A. These alterations in pharmacokinetic parameters allow PEG-Intron to be administered as a once weekly injection compared to thrice weekly injections with INTRON A. PEG-Intron is cleared by both the kidneys and liver. Although dose reduction is not required in hepatic dysfunction or failure, patients with renal dysfunction should be closely monitored for interferon toxicity. The agent should be used with caution in patients with CrCl < 50 mL/min. No significant drug interactions have been noted with this compound.

This agent represents a new medication with respect to the VA National Formulary. The Hepatitis C Program is working in conjunction with the PBM to complete the required paperwork to request the addition of PEG-Intron to the National Formulary. If you wish to prescribe this medication prior to the National Review, you should follow your local VISN and institutional formulary rules. Please contact the appropriate pharmacy representative to assist with this process. Below is a summary of key information that may help you and your pharmacy colleagues with procuring and using this product.

Clinical Data

The approval of PEG-Intron was based on a single randomized pivotal trial conducted in 1219 treatment-naïve patients with chronic HCV infection. Three doses of PEG-Intron (0.5, 1.0, 1.5 ug/kg weekly) were compared to INTRON A (3 MIU TIW) for 48 weeks of treatment. Comparative response was determined by measuring HCV RNA at 6 months post-treatment, which was defined as Sustained Virologic Response (SVR). The following table summarizes the comparative SVR rates from this study stratified by HCV genotype.

	INTRON A 3 MIU	**PEG-Intron 0.5 ug/kg**	**PEG-Intron 1.0 ug/kg**	**PEG-Intron 1.5 ug/kg**
Genotype 1	6%	11%	14%	14%
Genotype 2/3	28%	35%	47%	47%

Significant increases in SVR were seen only with doses PEG-Intron 1.0 and 1.5 ug/kg versus INTRON A. Normalization of ALT was greater with all doses of PEG-Intron but only achieved significance with the two higher doses. There was no significant difference between the response rates 1.0 and 1.5 ug/kg doses. Based on this data, the FDA approved PEG-Intron as a monotherapy for the treatment of chronic HCV at a dose of 1.0 ug/kg for 48 weeks of therapy.

Adverse Effects

As both products contain interferon alfa-2b, the adverse effect profile is similar and appropriate caution should be used when administering either of these two agents. Warnings exist for both products with regards to causing or aggravating neuropsychiatric, autoimmune, ischemic cardiac and infectious disorders. Several adverse events occurred at a higher rate with PEG-Intron administration compared to INTRON A. These include flu-like symptoms (46 vs. 38%), fever (22% vs. 12%) and injection site reactions (47% vs. 20%). Neutrophil and platelet counts decreased in 70% and 20% of treated patient respectively but only reached critical values in less than 1% of patients. Similar standard dose reduction guidelines for neutropenia and thrombocytopenia exist for both PEG-Intron and INTRON A. However, the reversal of these blood dyscrasias resolves more slowly with PEG-Intron and should be considered in patient management. Please consult the PEG-Intron product information insert for specific adverse effect reports and toxicity management guidelines.

Clinical Indications and Future Considerations

Currently, PEG-Intron is approved for the treatment of chronic HCV infection as monotherapy in treatment naive patients greater than 18 years old. Treatment is contraindicated in patients with autoimmune hepatitis and decompensated liver diseases. It should be noted the clinical results of PEG-Intron monotherapy are still inferior to the current standard of combination therapy Rebetron™ (interferon alfa-2b plus ribavirin). Therefore, the primary role for PEG-Intron monotherapy remains as an alternative for patients who are unable to tolerate or in whom ribavirin is contraindicated. The safety and efficacy of PEG-Intron in combination with ribavirin is currently under review at the FDA, with expected approval in early 2002. Furthermore, ribavirin (Rebetol™) is currently under review as a supplemental New Drug Application and may be unbundled and available for prescribing as early as May 2001.

Pharmacy Information

PEG-Intron is lyophilized powder that must be reconstituted prior to injection and is stable only for 24 hours after reconstitution. Both the diluent and drug are for single use only. Syringes and alcohol swabs are included with each unit dose. Specific instructions for patient self-administered injection of PEG-Intron are outlined in the accompanying Patient Management Guide and should be carefully reviewed by providers and patients. The following table contains relevant information to provide to Pharmacy Services for procuring this product.

Unit Dose Strength	NDC	Recommended Weight Range for Vial Size
100 ug/ml	0085-1368-01	37-56 kg
160 ug/ml	0085-1291-01	57-88 kg
240 ug/ml	0085-1304-01	89-136 kg
300 ug/ml	0085-1279-01	137-160 kg

The projected cost of treatment for 6 months is $4331.52-$5014.32 and for 12 months is $8663.04-$10,028.64.

If you require additional information on this product, please contact your local Schering Oncology-Biotech representative or the company's website at http://www.sch-plough.com. For questions regarding this letter or other pharmacy issues related to hepatitis C, please contact Stephen Rossi, Pharm.D., at the VA San Francisco Hepatitis C Center of Excellence at stephen.rossi@med.va.gov.