National PBM Drug Monograph

Peginterferon alfa-2a (40D) Pegasys®

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

November 2002

Introduction

Caveats remain in the management of Hepatitis C. Although interferon alfa 2b and ribavirin have become standard of care for most patients, this regimen fails to produce a sustained virologic response (SVR, as defined by the absence of detectable HCV RNA in the serum as shown by a qualitative HCV RNA assay with a lower limit of detection of 50 IU/ml or less at 24 weeks after the end of treatment) in many patients.[1] Pegylated interferons were developed to offer improved pharmacokinetics resulting in a prolonged duration of biological activity. Trials comparing standard interferon alfa 2b and pegylated interferon documented a larger percentage of patients with SVR in the pegylated interferon treatment group.[2,3,4,6] This may be the result of the increased duration of biological activity pegylated interferon displays over nonpegylated interferon. Tolerability of the pegylated interferons is comparable to the nonpegylated formulations.

Pharmacology/Pharmacokinetics[5,6]

Peginterferon alfa-2a (40D) effects its action by binding to receptors on specific target cells. Once these receptor cells are activated macrophages, natural killer cells, T helper and cytotoxic T cells are stimulated to enhance the host viral immune response.

The pegylation of interferon 2a with a 40D molecule resulted in a half-life approximately 10 times longer than standard interferon (77 versus 9 hours, respectively), a more sustained absorption with steady state being achieved in the first 5 to 8 weeks of therapy and a decreased clearance of the product. These factors allow for once weekly administration of the product. Additionally, these factors allow for a longer duration of biological activity, which may be key to an improved SVR in treated patients.[7,8]

Peginterferon alfa-2a (40D) is distributed in the blood and intersitial fluids. It is cleared from the body by hepatic and renal metabolism with the metabolites being excreted in both the urine and bile. The large molecular size and branched chain of the pegylated product result in reduced renal clearance and a prolonged exposure of the liver to the molecule.

The pharmacokinetic profile of peginterferon alfa-2a (40D) has been investigated in patients with renal impairment, chronic hepatitis C with cirrhosis and in geriatric patients.[9] It does not appear that dosage adjustments are necessary in any of these populations except in patients with end stage renal disease undergoing hemodialysis since there can be a 25% to 45% reduction in clearance.

FDA Approved Indication(s) and Off-label Uses

Peginterferon alpha-2a has been approved for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not been treated with interferon alfa.

Current VA National Formulary Status

Currently available interferon products for the treatment of HCV on National Formulary include: interferon alpha, interferon alfacon, interferon alpha 2b with ribavirin, and peg interferon alpha 2b,

Dosage and Administration[5,6]

The optimal dose of peginterferon alpha-2a (40D) is 180 µg injected subcutaneously once weekly. The recommended treatment duration is 48 weeks. Some clinical trials suggest that SVR can be predicted based on early virologic response rates at week 12 of treatment SVR is unlikely to be achieved when <2 log drop in viral load has not occurred by week 12 and discontinuation of therapy should be considered.

Patients must have laboratory monitoring while receiving any type of interferon therapy. If the neutrophil count < 750 cells/mm^3, the dose should be reduced to 135 µg. If the platelet count is < 50,000 cells/mm^3 the dose should be reduced to 90 µg. Therapy should be discontinued if the ANC is < 500 cells/mm^3 or the platelet count is < 25,000 cells/mm^3.

In patients with end-stage renal disease requiring hemodialysis, dose reduction to 135 ug is recommended. In renally impaired patients with a creatinine clearance <50 mL/min, peginterferon alpha-2a should be used with caution. Signs and symptoms of toxicity should be monitored.

If patients experience adverse clinical events (flu like symptoms, myalgia, depression, fatigue, anxiety) the dose may be reduced to 135 µg with a further decrease to 90 µg if required.

Adverse Effects (Safety Data)[5,6]

The side effect profile of peginterferon alpha-2a (40D) is similar to that of standard interferon. The majority of adverse effects reported by patients include: headache, fatigue, myalgia, pyrexia, rigors, arthralgia, nausea, alopecia, insomnia, diarrhea, depression and injection site reactions. In the clinical trial treatment groups, approximately 10% of patients receiving any type of interferon therapy terminated therapy early due to adverse events. The percent of patients with early withdrawal was not different among treatment groups.

Dosage modification was necessary in approximately 20-25% of patients receiving 180µg of peginterferon alpha-2a (40D). These modifications were most commonly attributed to neutropenia.

Table 1 compares the pooled adverse events from the clinical trials of peginterferon alpha-2a (40D) and standard interferon.

Table 1. Adverse events reported in clinical trials of peginterferon alpha-2a (40D) and standard interferon.

Adverse events	Peg interferon 2a (40D) 180µg N=559 (%)	Standard interferon 3 MIU or 6/3MIU N=554(%)
Gastrointestinal		
Nausea	23	30
Diarrhea	16	16
Abdominal pain	15	15
General		
Fatigue	50	50
Pyrexia	36	41
Rigors	32	42
Injection site reaction	22	18
Pain	11	12
Hematologic		
Neutropenia	21	8
Thrombocytopenia	5	2
Neurological		
Headache	54	58
Insomnia	19	23
Dizziness	16	12
Concentration impairment	8	10
Psychiatric		
Depression	18	19
Irritability	13	17
Anxiety	6	5

Precautions/Contraindications[5]

Peginterferon alfa-2a (40D) has a black box warning in its package insert regarding the potential of the agent to cause or aggravate fatal or life threatening neuropsychiatric, autoimmune ischemic or infectious disorders. Management of these adverse effects is discontinuation of the drug, usually resulting in reversal of the event.

The agent is contraindicated in patients with hypersensitivity to alfa-interferons, *E. coli* derived agents and any of the product components. The product contains benzyl alcohol; therefore, administration to neonates and infants should be avoided. Patients with autoimmune hepatitis or decompensated hepatic disease are not candidates for therapy.

The likelihood of neutropenia and thrombocytopenia increases when peginterferon alfa-2a (40D) is combined with ribavirin. Patients should be monitored during therapy and the doses of the agents adjusted accordingly.

Drug Interactions

The effects of peginterferon alfa-2a (40D) on the cytochrome P450 system have been investigated in normal volunteers. No significant effects were noted on the 2C9, 2C19, 2D6 or 3A4 isoenzymes in the cytochrome system. A decreased clearance of theophylline has been shown with concurrent peginterferon alfa-2a (40D) administration. This interaction is also well documented with standard interferon and is a result of inhibition in the CYP1A2 pathway. Thus, theophylline levels may need to be monitored and the dose adjusted accordingly.

Clinical Trials[8,10,11,12]

<table>
<tr><td>Citation</td><td>Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666-1672.</td></tr>
<tr><td>Study Goals</td><td>To determine the efficacy and safety of peginterferon alfa-2a once weekly with the efficacy and safety of interferon alfa-2a three times weekly treated for 48 weeks.</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Phase III clinical trial
➢ Parallel-dose, randomized
➢ Multicenter
➢ Treatment with either peginterferon alfa-2a 180µg once weekly for 48 weeks or interferon alfa-2a 6MU three times weekly for 12 weeks, then 3 MU three times weekly for 36 weeks
• Data Analysis
➢ Equivalence was defined as SVR no less than 5% of that seen in control group
➢ Peginterferon alfa-2a would be deemed superior to standard interferon if the lower limit of the 95% CI was greater than 1
➢ Intention to treat
➢ Cochran-Mantel-Haenszel
➢ Assumed SVR of 25% in standard interferon group, 35% in peginterferon group</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Treatment naïve
➢ HCV RNA level > 2000 copies/ml on polymerase chain reaction
➢ ALT above normal limits on 2 occasions
➢ Liver biopsy in previous year with documented findings consistent with chronic HCV
• Exclusion criteria
➢ Neutropenia <1500/mm ^{3} , thrombocytopenia < 90,000/ mm ^{3}
➢ Creatinine more than 1.5 times the upper limit of normal
➢ Coinfection with hepatitis A or B, HIV
➢ Decompensated liver disease, organ transplant, neoplastic disease, psychiatric disease</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>N</th><th colspan="2">% (N) Response at 48 weeks</th><th colspan="3">% (N) Sustained response at 24 week followup</th></tr>
<tr><td></td><td></td><td>Virologic</td><td>Biochemical</td><td>Virologic</td><td>Biochemical</td><td>Histologic</td></tr>
<tr><td>Peg IFN</td><td>267</td><td>69(185)*</td><td>46(123)</td><td>39(103)*</td><td>45(120)*</td><td>63</td></tr>
<tr><td>Std IFN</td><td>264</td><td>28(73)</td><td>39(104)</td><td>19(50)</td><td>25(65)</td><td>55</td></tr>
</table>
Virologic- undetectable plasma levels of HCV RNA (100 copies/ml at 24 and 72 weeks)
Biochemical-normalization of ALT levels
Histologic- ≥2 point improvement in the histological activity index score

* p≤0.001</td></tr>
<tr><td>Conclusions</td><td>In patients with chronic HCV, a regimen of peginterferon alfa-2a once weekly is more effective than interferon alfa-2a given three times weekly</td></tr>
<tr><td>Critique</td><td>• Strengths
• Multicenter with European and North American sites
• Defined laboratory endpoints
• Histology determined by single blinded investigator
• Patient population included those with and without cirrhosis
• Limitations
• Higher relapse rate in patients who received peginterferon therapy</td></tr>
<tr><td>Funding</td><td>Hoffman-LaRoche</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Heathcote EJ, Shiffman ML, Cooksley GE, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;343:1673-1680.</td></tr>
<tr><td>Study Goals</td><td>To examine the safety and efficacy of peginterferon alfa-2a compared to interferon alfa-2a in patients with HCV and cirrhosis or bridging fibrosis.</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Open label, randomized, parallel dose
➢ Multicenter
➢ Interferon alfa-2a 3 MU three times weekly, peginterferon alfa-2a 90 or 180 µg once weekly
➢ Study drug for 48 weeks then followed for an additional 24 weeks
➢ Primary outcome- SVR and biochemical response
➢ Data Analysis
➢ Cochran-mantel-Haenszel
➢ Two sided significance at 0.025 for pair wise comparisons</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Treatment naïve
➢ ALT above normal limits on 2 occasions
➢ Liver biopsy in previous year
• Exclusion criteria
➢ Neutropenia <1500/mm ^{3,} thrombocytopenia < 75,000/ mm ^{3}
➢ Alpha-fetoprotein above 100ng/ml
➢ Coinfection with HIV
➢ Decompensated liver disease, organ transplant, neoplastic disease, psychiatric disease</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>N</td><td colspan="2">% (N) Response at 48 weeks</td><td colspan="3">% (N) Sustained response at 24 week followup</td></tr>
<tr><td></td><td></td><td>Virologic</td><td>Biochemical</td><td>Virologic</td><td>Biochemical</td><td>Histologic</td></tr>
<tr><td>Peg IFN 90 µg</td><td>96</td><td>42(40)**</td><td>35(34)*</td><td>15(14)</td><td>20(19)</td><td>44(27/61)</td></tr>
<tr><td>Peg IFN 180 µg</td><td>87</td><td>44(38)**</td><td>39(34)*</td><td>30(26)**</td><td>34(30)**</td><td>54(37/69)*</td></tr>
<tr><td>Std IFN</td><td>88</td><td>14(12)</td><td>22(19)</td><td>8(7)</td><td>15(13)</td><td>31(17/55)</td></tr>
</table>
Virologic- undetectable plasma levels of HCV RNA (100 copies/ml at 24 and 72 weeks)
Biochemical-normalization of ALT levels
Histologic- ≥2 point improvement in the histological activity index score

* p≤0.05 ** p≤0.009 compared to interferon alfa-2a</td></tr>
<tr><td>Conclusions</td><td>In patients with HCV and cirrhosis or bridging fibrosis, peginterferon alfa-2a 180µg once weekly resulted in increased SVR and greater histologic improvement compared to standard interferon therapy.</td></tr>
<tr><td>Critique</td><td>• Strengths
• Patient with cirrhosis and fibrosis included
• Defined laboratory endpoints
• Limitations
• No clear reason for doses of peginterferon used</td></tr>
<tr><td>Funding</td><td>Hoffman –LaRoche</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Reddy RK, Wright TL, Pockros PJ, et al. Efficacy and safety of pegylated (40-kd) interferon α2a compared with interferon α2a in non-cirrhotic patients with hepatitis C. Hepatology 2001;33:433-438.</td></tr>
<tr><td>Study Goals</td><td>Compare the safety and efficacy of pegylated interferon at doses of 45,90,180,or 270µg once weekly to standard interferon alfa 2a.</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Phase II study
➢ Parallel-dose, randomized
➢ Multicenter
➢ 48 week duration
• Data Analysis
➢
➢ Intention to treat
➢ Fisher’s exact test
➢</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Treatment naïve
➢ ALT above normal limits on 2 occasions
➢ Liver biopsy in previous year
• Exclusion criteria
➢ Neutropenia <1500/mm ^{3,} thrombocytopenia < 90,000/ mm ^{3}
➢ Creatinine more than 1.5 times the upper limit of normal
➢ Coinfection with hepatitis A or B, HIV
➢ Decompensated liver disease, organ transplant, neoplastic disease, psychiatric disease</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>N</td><td colspan="2">% (N) Response at 48 weeks</td><td colspan="3">% (N) Sustained response at 24 week followup</td></tr>
<tr><td></td><td></td><td>Virologic</td><td>Biochemical</td><td>Virologic</td><td>Biochemical</td><td>Histologic</td></tr>
<tr><td>Peg IFN 45 µg</td><td>20</td><td>30(6)</td><td>20(4)</td><td>10(2)</td><td>10(2)</td><td>47(7)</td></tr>
<tr><td>Peg IFN 90 µg</td><td>20</td><td>45(9)*</td><td>20(4)</td><td>30(6)**</td><td>25(5)</td><td>59(10)</td></tr>
<tr><td>Peg IFN 180 µg</td><td>45</td><td>60(27)**</td><td>38(17)*</td><td>36(16)**</td><td>38(17)**</td><td>63(19)</td></tr>
<tr><td>Peg IFN 270 µg</td><td>41</td><td>56(23)***</td><td>27(11)</td><td>29(12)**</td><td>27(11)</td><td>66(19)</td></tr>
<tr><td>Std IFN</td><td>33</td><td>12(4)</td><td>15(5)</td><td>3(1)</td><td>9(3)</td><td>57(13)</td></tr>
</table>
Virologic- undetectable plasma levels of HCV RNA (100 copies/ml at 24 and 72 weeks)
Biochemical-normalization of ALT levels
Histologic- ≥2 point improvement in the histological activity index score

* p≤0.05 ** p≤0.009 ***p≤0.00009 compared to interferon alfa-2a</td></tr>
<tr><td>Conclusions</td><td>End of treatment virologic response and SVR were significantly better with 90,180 or 270 µg once weekly of pegylated interferon than standard interferon.</td></tr>
<tr><td>Critique</td><td>• Strengths
Defined laboratory endpoints</td></tr>
<tr><td>Funding</td><td>• Funded by Hoffman –LaRoche</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C. N Engl J Med 2002;347:975-982.</td></tr>
<tr><td>Study Goals</td><td>Determine whether peginterferon alfa-2a plus ribavirin is better than peginterferon alone or standard interferon plus ribavirin in the treatment of hepatitis C.</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Randomized, controlled, multicenter
➢ Randomization stratified by genotype and country
➢ Treatment with either peginterferon alfa-2a 180µg once weekly with placebo or ribavirin for 48 weeks or interferon alfa-2b 3MU three times weekly and ribavirin for 48 weeks
➢ Ribavirin orally dosed at 100mg per day if weight <75 kg and 1200 mg per day in >75 kg.
➢ Primary efficacy was SVR
• Data Analysis
➢ List information on power analysis and statistical tests utilized in the trial</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Treatment naïve
➢ HCV RNA level > 2000 copies/ml on polymerase chain reaction
➢ ALT above normal limits within the last six months
➢ Liver biopsy in previous year with documented findings consistent with chronic HCV
• Exclusion criteria
➢ Neutropenia <1500/mm ^{3,} thrombocytopenia < 90,000/ mm ^{3,} hemoglobin <12g/dl in women, 13 g/dl in men
➢ Creatinine more than 1.5 times the upper limit of normal
➢ Coinfection with hepatitis A or B, HIV
➢ Decompensated liver disease, organ transplant, neoplastic disease, psychiatric disease
➢ Drug dependence in the year preceding the study</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th></th><th>N</th><th>% Response at 48 weeks</th><th>% Sustained response at 24 week followup</th></tr>
<tr><td></td><td></td><td>Virologic</td><td>Virologic</td></tr>
<tr><td>Peg IFN ribavirin</td><td>453</td><td>69**, *</td><td>56**</td></tr>
<tr><td>Peg IFN placebo</td><td>224</td><td>59#</td><td>29**</td></tr>
<tr><td>Std IFN ribavirin</td><td>444</td><td>52</td><td>44**</td></tr>
</table>
Virologic- undetectable plasma levels of HCV RNA (100 copies/ml at 24 and 72 weeks)
*p=0.01Peg IFN /ribavirin vs Peg IFN/placebo
** p<0.001 Peg IFN/ribavirin vs. Std IFN/ribavirin
#p=0.06 Peg IFN/placebo vs. Std IFN/ribavirin

Among patients with HCV genotype 1 and high baseline RNA levels, 41% vs. 33% had an SVR (Peg IFN/ribavirin vs. IFN/ribavirin p<0.001)</td></tr>
<tr><td>Conclusions</td><td>Peginterferon alfa-2a plus ribavirin was tolerated as well as standard interferon and ribavirin. A significant improvement on SVR was seen with the combination of peginterferon and ribavirin over standard interferon/ribavirin or peginterferon alone.</td></tr>
<tr><td>Critique</td><td>• Strengths
• Addressed significance of genotype
• Used weight based ribavirin dosing
• Analyzed predicted response based on week 12 RNA levels</td></tr>
<tr><td>Funding</td><td>• Partial funding from Hoffman-LaRoche</td></tr>
</table>

Acquisition Costs

Generic	Trade name	fss_price	valpkg	va_ppu
INTERFERON ALFA_2A RECOMBINANT180MCG/VIL	PEGASYS 180 MCG/ML	$166.70	1	$166.70
INTERFERON ALFA-2B,RECOMBINANT 100MCG/VIL	PEG INTRON 100MCG/ML POWD F/INJ VIA	$148.88	1	$148.8800
INTERFERON ALFA-2B,RECOMBINANT 160MCG/VIL	PEG INTRON 160MCG/ML POWD F/INJ VIA	$156.18	1	$156.1800
INTERFERON ALFA-2B,RECOMBINANT 240MCG/VIL	PEG INTRON 240MCG/ML POWD F/INJ VIA	$163.68	1	$163.6800
INTERFERON ALFA-2B,RECOMBINANT 300MCG/VIL	PEG INTRON 300MCG/ML POWD F/INJ VIA	$171.54	1	$171.5400
REBETRON 1000/MDV PKT (1236-02)	REBETRON COMBINATION THERAPY PAK 10	$390.44	1	$390.4400
REBETRON 1000/PAK 3 PKT (1241-02)	REBETRON COMBINATION THERAPY PAK 10	$398.58	1	$398.5800
REBETRON 1000/PEN PKT (1258-02)	REBETRON COMBINATION THERAPY PAK 10	$388.27	1	$388.2700
REBETRON 1200/MDV PKT (1236-01)	REBETRON COMBINATION THERAPY PAK 12	$431.80	1	$431.8000
REBETRON 1200/PAK 3 PKT (1241-01)	REBETRON COMBINATION THERAPY PAK 12	$437.24	1	$437.2400
REBETRON 1200/PEN PKT (1258-01)	REBETRON COMBINATION THERAPY PAK 12	$435.27	1	$435.2700
REBETRON 600/MDV PKT (1236-03)	REBETRON COMBINATION THERAPY PAK 60	$325.20	1	$325.2000
REBETRON 600/PAK 3 PKT (1241-03)	REBETRON COMBINATION THERAPY PAK 60	$321.96	1	$321.9600
REBETRON 600/PEN PKT (1258-03)	REBETRON COMBINATION THERAPY PAK 60	$320.14	1	$320.1400
RIBAVIRIN 200MG CAP	REBETOL 200MG CAP	$255.85	42	$6.0917
RIBAVIRIN 200MG CAP	REBETOL 200MG CAP	$512.05	84	$6.0958
RIBAVIRIN 200MG CAP	REBETOL 200MG CAP	$341.45	56	$6.0973
RIBAVIRIN 200MG CAP	REBETOL 200MG CAP	$426.82	70	$6.0974

Cost Analysis

	Cost per week
Monotherapy	
Peginterferon alfa 2b 1.0ug/kg/week	$152.59
Peginterferon alfa 2a 180ug/week	$166.70
Combination Therapy	
Peginterferon alfa 2b 1.5 ug/kg/week Ribavirin 800 mg QD	$326.80
Peginterferon alfa 2a 180ug/week Ribavirin 800 mg QD	$337.22
Peginterferon alfa 2b 1.5 ug/kg/week Ribavirin 1000 mg QD	$368.52
Peginterferon alfa 2a 180ug/week Ribavirin 1000 mg QD	$379.85
Interferon alfa 2a 3 MU TIW Ribavirin 1000 mg QD	$189.67

Doses based on 70 kg patient

Data Compilation Tables

	Drug	Drug
	Heathcote[9], pegIFN 180 µg vs IFN A 3 MU SVR at 48 weeks	Zezum[10], pegIFN 180 µg vs IFN A 6 MU then 3 MU SVR at 48 weeks
Relative Risk Reduction	0.35	0.71
Absolute Risk Reduction	30	51
NNT	3	1.9

Conclusions

Peginterferon alfa-2a (40kD) has demonstrated increased efficacy, as measured by SVR, in comparison to standard interferon in patients who are treatment naïve, patients with hard to treat HCV (genotype 1) and in cirrhotic and non-cirrhotic patients. These improved results were seen without compromising the safety or tolerability profile of the agent. Indeed, peginterferon alfa-2a (40kD) may improve patient compliance as the agent is dosed weekly in comparison to three times weekly with standard interferon regimens. The use of peginterferon alfa-2a (40kD) monotherapy appears to exhibit a similar response to standard interferon/ribavirin combination therapy. These findings need to be exhibited in further comparative trials but may afford alternatives for patients who cannot tolerate ribavirin therapy.

Recommendations

Peginterferon alfa-2a (40kD) has proven safety and efficacy in the treatment of hepatitis C. In particularly difficult populations, such as those with genotype 1 and/or compensated cirrhosis, the agent displays significant responses in virologic, biochemical and histologic outcomes. Peginterferon alfa-2a (40kD) should be added to the National Formulary and criteria for its use developed, which will define specific populations and outcomes for its use.

References:

[1] Booth JCL, O'Grady J, Neuberger J, et al. Clinical Guidelines on the management of hepatitis C. Gut 2001;49 suppl I:I1-21.

[2] Wang Y, Youngster S, Grace M, et al. Structural and biological characterization of pegylated recombinant interferon alpha-2b and its therapeutic implications. Advanced Drug Del Rev 2002;54:547-570.

[3] Kjaergard LL, Krogsgaard K, Gluud C. Interferon alfa with or without ribavirin for chronic hepatitis C:systemic review of randomized trials. BMJ 2002;323:1151-1155.

[4] Perry CM, Jarvis B. Peginterferon-α- 2a(40kD) A review of its use in the management of chronic hepatitis C. Drugs 2001;61(15):2263-2288.

[5] Product information Pegasys® (peginterferon alfa-2a). Roche Pharmaceuticals Nutley, NJ. October 2002.

[6] Reddy KJ, Modi MW, Pedder S. Use of peginterferon alfa-2a(40 KD) (Pegasys®) for the treatment of hepatitis C. Advanced Drug Del Rev 2002;54:571-586.

[7] Modi MW, Fried M, Reindollar RW, et al. The pharmacokinetic behavior of pegylated (40kDa) interferon alfa-2a in chronic hepatitis C patients after multiple dosing.(abstract) Hepatology 2000a;32(4 pt 2):394A.

[8] Xu Z, Hoffman J, Patel I, Joubert P. Single dose safety/tolerability and pharmacokinetics/pharmacodynamics following administration of ascending subcutaneous doses of pegylated interferon (PEG-IFN) and interferon afla-2a to healthy subjects (abstract). Hepatology 1998;28(suppl):702A

[9] Heathcote EJ, Shiffman ML, Cooksley GE, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;343:1673-1680.

[10] Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666-1672.

[11] Reddy RK, Wright TL, Pockros PJ, et al. Efficacy and safety of pegylated (40-kd) interferon α2a compared with interferon α2a in non-cirrhotic patients with hepatitis C. Hepatology 2001;33:433-438.

[12] Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C. N Engl J Med 2002;347:975-982.

Prepared by: Kathryn Tortorice, Pharm D, BCPS
Reviewed by: Matt Goetz M.D. and Helen Yee Pharm D
Date: November 12, 2002