PEG INTRON is a new drug registered in 2002. Information below is updated information from 2009.

**PEG-INTRON® Pen**
*(PegInterferon alfa-2b)*
*Solution for Injection*

**DESCRIPTION:** PEG-INTRON® PEN is available in strengths of 50 micrograms, 80 micrograms, 100 micrograms, 120 micrograms, and 150 micrograms powder and solvent for solution for injection in pre-filled pens.

Peginterferon alfa-2b is a conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. When reconstituted with solvent as recommended, each pre-filled PEG-INTRON® PEN provides 0.5 ml of solution containing either 50 micrograms, 80 micrograms, 100 micrograms, 120 micrograms or 150 micrograms.

PEG-INTRON® PEN also contains as excipients anhydrous disodium phosphate, dihydrate sodium dihydrogen phosphate, sucrose and polysorbate 80. The solvent provided for parenteral use is sterile water for injection.

The deliverable volume from PEG-INTRON® PEN is 0.5 ml. An overfill is included for proper dispensing from the pen delivery system.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics properties**

Pharmacotherapeutic, Immunostimulants, Cytokines and immunomodulators, Interferons, group Peginterferons alfa-2b, ATC code: L03A B10.

PEG-INTRON® is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

**Interferon alfa-2b**
Recombinant interferon alfa-2b is obtained from a clone of *E.coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

*In vitro* and *in vivo* studies suggest that biological activity of PEG-INTRON® is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity lymphocytes for target cells. Any or all of these activities may contribute to interferon’s therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

**PEG-INTRON®**

PEG-INTRON® pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature concentrations of effector proteins such as serum neopterin and 2’-5’-oligoadenylate synthetase (2’5’-OAS), as well as white cell and neutrophil counts. Subjects treated with PEG-INTRON® showed mild dose-related elevations in body temperature. Following single doses of PEG-INTRON® between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose related manner. Neutrophil and white cell count reduction at the end of week 4 correlated with the dose of PEG-INTRON®.

**PEG-INTRON® clinical trials**

I. Chronic Hepatitis C

A. Naive Patients

Two pivotal trials have been conducted, one (C/197-010) with PEG-INTRON® monotherapy; the other (C198-580) with PEG-INTRON® in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (≥ 100 copies/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis and abnormal serum ALT.
In PEG-INTRON® monotherapy trial, a total of 916 naive chronic hepatitis C patients were treated with PEG-INTRON® (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week [TIW] as a comparator. This study showed that PEG-INTRON® was superior to interferon alfa-2b.

In the PEG-INTRON® combination regimens trial, 1,530 naive patients were treated for one year with one of the following combination regimens:

- PEG-INTRON® (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n=511)
- PEG-INTRON® (1.5 micrograms/kg/week) for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n=514)
- Interferon alfa-2b (3 MIU TIW) + ribavirin (1,000/1,200 mg/day) (n=505).

In this trial, the combination of PEG-INTRON® (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (Table 1), particularly in patients infected with Genotype 1 (Table 2). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PEG-INTRON® or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (Table 2), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Response rates in this trial were increased if patients were able to maintain compliance. Regardless of genotype, patients who received the recommended combination regimen and received ≥ 80% of their treatment with PEG-INTRON® and ribavirin had a higher sustained response 6 months after 1 year of treatment than those who took < 80 % of their treatment (72% vs 46%).
<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>PEG-INTRON® monotherapy</th>
<th>PEG-INTRON® + ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P 1.5</td>
<td>304</td>
<td>511</td>
</tr>
<tr>
<td>P 1.0</td>
<td>297</td>
<td>514</td>
</tr>
<tr>
<td>P 0.5</td>
<td>315</td>
<td>504</td>
</tr>
<tr>
<td>I</td>
<td>303</td>
<td></td>
</tr>
<tr>
<td>Response at end of treatment</td>
<td>49%</td>
<td>65%</td>
</tr>
<tr>
<td>Sustained response</td>
<td>23%</td>
<td>54%**</td>
</tr>
</tbody>
</table>

P 1.5 PEG-INTRON 1.5 microgram/kg
P 1.0 PEG-INTRON 1.0 microgram/kg
P 0.5 PEG-INTRON 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PEG-INTRON (1.5 microgram/kg) + ribavirin (800 mg)
P 0.5/R PEG-INTRON (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

* p < 0.001 P 1.5 vs I
** p = 0.0143 P 1.5/R vs IR
Table 2 Sustained response rates with PEG-INTRON® + ribavirin (by ribavirin dose, genotype and viral load)

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Ribavirin dose (mg/kg)</th>
<th>P 1.5/R</th>
<th>P 0.5/R</th>
<th>I/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10.6</td>
<td></td>
<td>54 %</td>
<td>47 %</td>
<td>47 %</td>
</tr>
<tr>
<td>&gt; 10.6</td>
<td></td>
<td>50 %</td>
<td>41 %</td>
<td>27 %</td>
</tr>
<tr>
<td>Genotype 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10.6</td>
<td></td>
<td>42 %</td>
<td>34 %</td>
<td>33 %</td>
</tr>
<tr>
<td>&gt; 10.6</td>
<td></td>
<td>38 %</td>
<td>25 %</td>
<td>20 %</td>
</tr>
<tr>
<td>Genotype 1 ≤ 600,000 IU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10.6</td>
<td></td>
<td>73 %</td>
<td>51 %</td>
<td>45 %</td>
</tr>
<tr>
<td>&gt; 10.6</td>
<td></td>
<td>74 %</td>
<td>25 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Genotype 1 &gt; 600,000 IU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10.6</td>
<td></td>
<td>30 %</td>
<td>27 %</td>
<td>29 %</td>
</tr>
<tr>
<td>&gt; 10.6</td>
<td></td>
<td>27 %</td>
<td>25 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Genotype 2/3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10.6</td>
<td></td>
<td>82 %</td>
<td>80 %</td>
<td>79 %</td>
</tr>
<tr>
<td>&gt; 10.6</td>
<td></td>
<td>79 %</td>
<td>73 %</td>
<td>50 %</td>
</tr>
</tbody>
</table>

P 1.5/R PEG-INTRON (1.5 microgram/kg) + ribavirin (800 mg)
P 0.5/R PEG-INTRON (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PEG-INTRON monotherapy study, the quality of life was generally less affected by 0.5 microgram/kg of PEG-INTRON than by either 1.0 microgram/kg of PEG-INTRON once weekly or 3 MIU of interferon alfa-2b TIW.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (≤ 2,000,000 copies/ml) received PEG-INTRON®, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50%. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at Week 4 and Week 24 of therapy. In this subgroup, there was 92% (89/97) sustained virological response rate. The high sustained response rate in the subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48). Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

HCV/HIV Co-infected patients
Two trials have been conducted in patients coinfected with HIV and HCV. The response to treatment in both of these trials is presented in Table 3. Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either peginterferon alfa-2b (1.5 µg/kg/week) plus ribavirin (800mg/day) or interferon alfa-2b (3 MIU
Tiw) plus ribavin (800 mg/day) for 48 weeks with a follow up period of 6 months. Study 2 (P02080) was randomized, single center study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were coinfected with HIV. Patients were randomized to receive either PEG-INTRON® (100 or 150 µg/week based on weight) plus ribavin (800-1200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavin (800-1200 mg/day based on weight). The duration of therapy was 48 weeks with a follow up period of 6 months except for patients infected with genotypes 2 or 3 viral load <800,000 IU/ml (Amplicor) who were treated 24 weeks with a 6 month follow up period.

### Table 3 Sustained virological response based on genotype after peginterferon alfa-2b in combination with Ribavirin in HIV/HCV Co-infected patients

<table>
<thead>
<tr>
<th></th>
<th>Study 1¹</th>
<th>Study 2²</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>peginterferon alfa-2b (1.5 µg/kg/week) + ribavin (800mg)</td>
<td>interferon alfa-2b (3 MIU TIW) + ribavin (800mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>27% (56/205)</td>
<td>20% (41/205)</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>Genotype 1, 4</td>
<td>17% (21/125)</td>
<td>6% (8/129)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Genotype 2, 3</td>
<td>44% (35/80)</td>
<td>43% (33/76)</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

**a**: p value based on Cochran-Mantel Haenszel Chi square test.  
**b**: p value based on chi-square test.  
**c**: subjects <75kg received 100µg/week peginterferon alfa-2b and subjects ≥75kg received 150µg/week peginterferon alfa-2b.  
**d**: ribavirin dosing was 800 mg for patients <60kg, 1000 mg for patients 60-75kg, and 1200 mg for patients >75kg.

MIU = million international units; TIW = three times a week.


**Histological response**

Liver biopsies were obtained before and after treatment of Study 1 and were available for 210 of the 412 subjects (51%). Both the Metavir score and Ishak grade decreased among subjects treated with peginterferon alfa-2b in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.
**B. PEG-INTRON®/ribavirin retreatment of prior treatment failures clinical trial**

In a non-comparative trial, 1336 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PEG-INTRON® 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at Treatment Week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post treatment (Table 4).

### Table 4 Rates of Response to Retreatment in Prior Treatment Failures

<table>
<thead>
<tr>
<th></th>
<th>interferon alfa 2b/Ribavirin</th>
<th>peginterferon alfa 2b/Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR% (n)</td>
<td>25 (255/1.030)</td>
<td>16 (48/299)</td>
</tr>
<tr>
<td>99%CI</td>
<td>21,28</td>
<td>11,22</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>45 (95/213)</td>
<td>36 (40/112)</td>
</tr>
<tr>
<td>Genotype 1/4</td>
<td>34 (52/154)</td>
<td>29 (24/83)</td>
</tr>
<tr>
<td>Genotype 2/3</td>
<td>73 (41/56)</td>
<td>55 (16/29)</td>
</tr>
<tr>
<td>NR</td>
<td>17 (117/673)</td>
<td>4 (7/172)</td>
</tr>
<tr>
<td>Genotype 1/4</td>
<td>13 (75/592)</td>
<td>4 (6/160)</td>
</tr>
<tr>
<td>Genotype 2/3</td>
<td>51 (40/78)</td>
<td>10 (1/10)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (138/825)</td>
<td>12 (28/243)</td>
</tr>
<tr>
<td>2/3</td>
<td>62 (103/166)</td>
<td>44 (17/39)</td>
</tr>
<tr>
<td>4</td>
<td>31 (10/32)</td>
<td>20 (3/15)</td>
</tr>
<tr>
<td>METAVIR Fibrosis score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>32 (92/289)</td>
<td>23 (15/66)</td>
</tr>
<tr>
<td>F3</td>
<td>27 (86/323)</td>
<td>17 (16/92)</td>
</tr>
<tr>
<td>F4</td>
<td>19 (77/416)</td>
<td>12 (17/141)</td>
</tr>
<tr>
<td>Baseline viral load</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVL (&gt;600,000 IU/ml)</td>
<td>21 (128/622)</td>
<td>9 (17/192)</td>
</tr>
<tr>
<td>LVL (&lt;600,000 IU/ml)</td>
<td>31 (127/406)</td>
<td>29 (30/105)</td>
</tr>
</tbody>
</table>

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.

Serum HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by central laboratory.

Overall, approximately 37% of patients had undetectable plasma HCV-RNA level at week 12 of
therapy measured using a research-based test (limit detection 125 IU/ml). In this subgroup, there was a 57% (282/499) sustained virological response rate. For patients with prior failure on therapy with non pegylated interferon or pegylated interferon and negative at Week 12, the sustained response rates were 59% and 47%, respectively. In patients with > 2 log viral reduction but detectable virus at Week 12, the estimated SVR is overall about 6%. Nonresponders to prior therapy with pegylated interferon/ribavirin were less likely to respond to retreatment than nonresponders to nonpegylated interferon/ribavirin (4% vs 17%).

Long-Term efficacy data
In a large study, 1,071 patients were enrolled after treatment in a prior non pegylated interferon alfa-2b or non pegylated interferon alfa-2b/Rebetol® study to evaluate the durability of sustained virologic response and assess the impact of continued viral negativity on clinical outcomes. 462 patients completed at least 5 years of long-term follow-up and only 12 sustained responders out of 492 relapsed during this study. The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 97% with a 95% Confidence interval of [95%, 99%].

SVR after treatment of chronic HCV with non pegylated interferon alfa-2b (with or without Rebetol®) results in long term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

II. Chronic Hepatitis B
Three keys studies in chronic hepatitis B have been conducted with PEG-INTRON®, all demonstrating efficacy and safety of PEG-INTRON® use either alone or in combination with lamivudine.

A randomized double-blind multi-centric international study by Janssen, et. al. published in Lancet v.365, Jan 2005, found that treatment with PEG-INTRON® is effective for HBeAg-positive chronic hepatitis B while combination with lamivudine did not increase efficacy (Table 5). 307 patients were randomized to be treated for 52 weeks with either PEG-INTRON® monotherapy (100 mcg/week for 32 weeks followed by 50mcg/week until end of treatment) or PEG-INTRON® combination with lamivudine (100 mg/day) for 52 weeks. Analyses were based on the modified intent-to-treat population of 266 patients, 21% of whom had prior interferon therapy and 13% had prior lamivudine therapy. The primary efficacy measure was sustained response indicated by loss of HBeAg at the end of 26 weeks follow up.

<table>
<thead>
<tr>
<th>Table 5: Response at the end of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined therapy n=130</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
</tbody>
</table>
| Virological response in serum |                  |   |}
<p>| HBeAg loss | 46 (35%) | 49 (36%) | 0.91 |
| HBeAg seroconversion | 38 (29%) | 39 (29%) | 0.92 |</p>
<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Lamivudine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV-DNA &lt;200 000 copies/ml</td>
<td>41 (32%)</td>
<td>37 (27%)</td>
<td>0.44</td>
</tr>
<tr>
<td>HBV-DNA &lt;4000 copies/ml</td>
<td>12 (9%)</td>
<td>9 (7%)</td>
<td>0.43</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>9 (7%)</td>
<td>9 (7%)</td>
<td>0.92</td>
</tr>
<tr>
<td>HBsAg seroconversion</td>
<td>9 (7%)</td>
<td>7 (5%)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Biochemical response in serum

<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Lamivudine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT normalized</td>
<td>46 (35%)</td>
<td>44 (32%)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

A Hong Kong study by H Chan et al, published in Annals of Int Med, vol. 142, Feb 2005, involved 100 treatment naive HBeAg-positive chronic hepatitis B patients who were randomized 1:1 to either a staggered regimen of combination with PEG-INTRON® (1.5 mcg/kg/week, maximum 100 mcg/week) given for 32 weeks plus lamivudine (100 mg daily) for 52 weeks or lamivudine (100 mg daily) alone for 52 weeks. The primary endpoint was sustained virologic response (HBeAg seroconversion and HBV DNA level <500 000 copies/ml) at 24 weeks follow up. The SVR was 36% for the combination and 14% for the lamivudine monotherapy, indicating a clear superiority when PEG-INTRON® is part of the treatment regimen.

Another 230 HBeAg-positive chronic hepatitis B patients in a study conducted at six centers in China (HBV-P02775) were randomized 1:1 to either PEG-INTRON® 1.0 mcg/kg/week or INTRON A (conventional interferon alfa-2b) 3 miu three times a week for 24 weeks. 87% of the patients enrolled were treatment naive while the remainder were relapsers to previous interferon therapy. 74% (170/230) of the patients in the study were of the more difficult to treat genotype C population. HBeAg loss at the end of the 24 week follow-up was found in 24% (28/115) of those treated with PEG-INTRON® vs 14% (16/115) of those treated with conventional interferon. In the genotype C subgroup, HBeAg loss was 18% and 8% for PEG-INTRON® and conventional interferon, respectively.

In the PEG-INTRON® monotherapy study, the quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PEG-INTRON® once weekly or 3 MIU of interferon alfa-2b TIW.

**Pharmacokinetics properties**
PEG-INTRON® is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PEG-INTRON® is free interferon alfa-2b. The biologic activity of pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentration occurs between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PEG-INTRON® C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by bioassay.

Mean (SD) PEG-INTRON® elimination half-life is approximately 40 hours (13.3 hours) with apparent clearance of 22.0 ml/hr kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30%) of PEG-INTRON® apparent clearance.

Renal function: Renal clearance appears to account for 30% of total clearance of PEG-INTRON®. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC and half-life increased in relation to degree of renal impairment.

Following multiple dose of PEG-INTRON® (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PEG-INTRON® is reduced by a mean of 17% in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by mean of 44% in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance similar in patients with severe renal.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PEG-INTRON®. Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PEG-INTRON®.
Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PEG-INTRON® following a single subcutaneous dose of 1.0 micrograms/kg were not affected by age. The data suggest that no alteration in PEG-INTRON® dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluation have not been performed on these patients. PEG-INTRON® is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralizing factors: Interferon neutralizing factor assay were performed on serum samples of patients who received PEG-INTRON® in the clinical trial. Interferon neutralizing factors are antibodies which neutralize the antiviral activity of interferon. The clinical incidence of neutralizing factors in patients who received PEG-INTRON® 0.5 micrograms/kg is 1.1%.

Preclinical safety data

PEG-INTRON®: Adverse events not observed in clinical trial were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PEG-INTRON® have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PEG-INTRON® is likely to also cause this effect. Effects on fertility have not been determined. PEG-INTRON® showed no genotoxic potential. (It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy).

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism in vivo has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in vitro mutagenicity assays.

PEG-INTRON® plus ribavirin: When used in combination with ribavirin, PEG-INTRON® did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anemia, the severity of which was greater than that produced by either active substance alone.

INDICATIONS AND USAGE:
PEG-INTRON® Injection is indicated for the treatment of chronic hepatitis C and chronic hepatitis B.

The optimal treatment for chronic hepatitis C is considered to be the administration of the combination of interferon alfa-2b with ribavirin. *When PEG-INTRON® Injection is to be used in combination with ribavirin, please refer also to ribavirin product information.*

This combination of peginterferon alfa-2b with ribavirin is indicated for the treatment of naive, relapse and nonresponder patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV. This combination is also indicated for the treatment of patients with chronic hepatitis C who are co-infected with clinically stable HIV.

Patients must be 18 years of age or older and have compensated liver disease and who are positive for serum HCV-RNA or anti-HCV.

**DOSAGE AND ADMINISTRATION**

0.36 – 1.08 x 10^5 International Units of PEG-INTRON® is equal to one (1) mcg of PEG-INTRON®.

**Chronic Hepatitis B:**
PEG-INTRON® Injection is administered subcutaneously at a dose of 1.0 to 1.5 microgram/kg once weekly for at least 24 weeks and up to 52 weeks. The dose should be selected based on the anticipated efficacy and safety. Patients with hard to treat genotype C & D may benefit from the higher dose and longer duration. Treatment with PEG-INTRON® should be initiated and monitored only by a physician experienced in the treatment of patients with hepatitis B.

When self-administration is recommended, the patient should be advised to vary the injection site each time the injection is administered.

**Chronic Hepatitis C:**

**MONOTHERAPY**
PEG-INTRON® PEN monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety. Treatment with PEG-INTRON® PEN should be initiated and monitored only by a physician experienced in the treatment of patients with hepatitis C. In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e. 1 year of treatment.

When self-administration is recommended, the patient should be advised to vary the injection site each time the injection is administered.

In patients who fail to show loss of HCV-RNA at 6 months, treatment with PEG-INTRON® PEN should be discontinued.

PEG-INTRON® monotherapy was not studied in HCV/HIV co-infected patients.

**COMBINATION THERAPY:**

PEG-INTRON® PEN 1.5 micrograms/kg/week subcutaneously in combination with ribavirin capsules.

The dose of ribavirin to be used in combination with PEG-INTRON® PEN is based on patient body weight (Table 6). Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

<table>
<thead>
<tr>
<th>Patient weight (kg)</th>
<th>Daily ribavirin dose</th>
<th>Number of 200 mg capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65</td>
<td>800 mg</td>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>65 - 85</td>
<td>1,000 mg</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>86 - 105</td>
<td>1,200 mg</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;105</td>
<td>1,400 mg</td>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>: 2 morning, 2 evening  
<sup>b</sup>: 2 morning, 3 evening  
<sup>c</sup>: 3 morning, 3 evening  
<sup>d</sup>: 3 morning, 4 evening

As an alternative to exact calculation of dose, a simplified PEG-INTRON® Powder for Solution for Injection dosage was developed based on experience in clinical trials (see Table 7). This table coordinates the PEG-INTRON® simplified dose by weight-based groups and relates that dose to the most appropriate pen presentation. The corresponding ribavirin capsule dose is also integrated.

PEG-INTRON® Powder for Solution for Injection is administered subcutaneously once weekly. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 7 - Dosing for Combination Therapy**
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>PEG-INTRON®</th>
<th>Ribavirin Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pen/Strength (µg/0.5ml)</td>
<td>Administer once weekly (ml)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>40-50</td>
<td>80</td>
<td>0.4</td>
</tr>
<tr>
<td>51-64</td>
<td>80</td>
<td>0.5</td>
</tr>
<tr>
<td>65-75</td>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td>76-85</td>
<td>120</td>
<td>0.5</td>
</tr>
<tr>
<td>86-105</td>
<td>150</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;105</td>
<td>150</td>
<td>0.5</td>
</tr>
</tbody>
</table>

a: 2 morning, 2 evening  
b: 2 morning, 3 evening  
c: 3 morning, 3 evening  
d: 3 morning, 4 evening

**Duration of treatment - Naive Patients:**

*Predictability of sustained virological response*: Patients infected with virus genotype 1 who fail to achieve virological response at week 12 are highly unlikely to become sustained virological responders (see also section 5.1).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks). In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment or pursued for an additional 24 weeks (i.e., overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- **Genotype 2 or 3**: It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.

- **Genotype 4**: In general, patients with infected genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

**HIV/HCV Co-infection**

The recommended duration of dosing for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.

*Predictability of response and non-response in HIV/HCV Co-infection*

Early virological response by Week 12, defined as a 2 log viral load decrease or undetectable levels of HCV RNA, has been shown to be predictive for sustained response. The negative
predictive value for sustained response in HIV/HCV co-infected patients treated with PEG-INTRON®/Ribavin was 99% (67/68; Study 1) (see section on clinical trials in HIV/HCV co-infected patients). A positive predictive value of 50% (52/104; Study 1) was observed for HIV/HCV co-infected patients receiving combination therapy.

Duration of treatment-Retreatment of Prior Treatment Failures (Relapse and Nonresponder Patients)

Predictability of sustained virological response: All relapse and non responder patients, irrespective of genotype, who have demonstrated undetectable serum HCV RNA at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response at week 12 are highly unlikely to become sustained virological responders (see also section on clinical trials in prior treatment failures).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PEG-INTRON® PEN or PEG-INTRON® PEN with ribavirin, modify the dosages of each product if appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification (see Dosage modification guidelines, Table 8a for PEG-INTRON® PEN and Table 8b for PEG-INTRON® PEN with ribavirin).

### Table 8a Dose modification guidelines for PEG-INTRON® PEN

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Reduce PEG-INTRON® PEN to one-half dose if:</th>
<th>Discontinue PEG-INTRON® PEN if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>$&lt; 0.75 \times 10^9$/l</td>
<td>$&lt; 0.5 \times 10^9$/l</td>
</tr>
<tr>
<td>Platelets</td>
<td>$&lt; 50 \times 10^9$/l</td>
<td>$&lt; 25 \times 10^9$/l</td>
</tr>
</tbody>
</table>

### Table 8b Dose modification guidelines for PEG-INTRON® Combination Therapy

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th>Reduce only Ribavirin dose to 600mg/day* if:</th>
<th>Reduce only PEG-INTRON® PEN dose to one-half dose if:</th>
<th>Discontinue PEG-INTRON® PEN combination therapy if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>$&lt; 10$ g/dl</td>
<td></td>
<td>$&lt; 8.5$ g/dl</td>
</tr>
<tr>
<td>Patients with history of stable cardiac disease</td>
<td>$\geq 2$ g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)</td>
<td></td>
<td>$&lt; 12$ g/dl after four weeks of dose reduction</td>
</tr>
<tr>
<td>White blood cells</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>-</td>
<td>$&lt; 0.75 \times 10^9$/l</td>
<td>$&lt; 0.5 \times 10^9$/l</td>
</tr>
<tr>
<td>Platelets</td>
<td>-</td>
<td>$&lt; 50 \times 10^9$/l</td>
<td>$&lt; 25 \times 10^9$/l</td>
</tr>
<tr>
<td>Bilirubin - direct</td>
<td>-</td>
<td></td>
<td>$2.5 \times$ ULN**</td>
</tr>
<tr>
<td>Bilirubin - indirect</td>
<td>$&gt; 5$ mg/dl</td>
<td></td>
<td>$&gt; 4$ mg/dl (for $&gt; 4$ weeks)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/AST</td>
<td>-</td>
<td></td>
<td>$2$ x baseline and $&gt; 10$ x ULN**</td>
</tr>
</tbody>
</table>

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening
** Upper limit of normal
Special populations
Use in renal impairment:

**Monotherapy:** PEG-INTRON® should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PEG-INTRON® should be reduced by 25%. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PEG-INTRON® reduced by 50%. Data are not available for the use of PEG-INTRON® in patients with creatinine clearance < 15 ml/minute. Patients with severe renal impairment, including dose on hemodialysis, should be closely monitored. If renal function decreases during treatment, PEG-INTRON® therapy should be discontinued.

**Combination therapy:** Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PEG-INTRON® PEN (See Contraindications and Pharmacokinetics). When PEG-INTRON® is administered in combination with REBETOL, subjects with impaired renal function and/or those over the age of 50 should be more carefully monitored with respect to the development of anemia.

It is recommended that renal function be evaluated in all patients prior to initiation of PEG-INTRON® PEN. Patients with moderate renal impairment should be closely monitored and should have their dose of PEG-INTRON® PEN reduced if medically appropriate. If serum creatinine rises to > 2 mg/dl (see Table 8b), PEG-INTRON® PEN must be discontinued (see Contraindications and Pharmacokinetics).

**Use in hepatic impairment:** The safety and efficacy of peginterferon alfa-2b has not been evaluated in patients with severe hepatic dysfunction. Therefore, PEG-INTRON® PEN must not be used in these patients.

**Use in the elderly (≥ 65 years of age):** There does not appear to be a significant age-related effect on the pharmacokinetics of PEG-INTRON® PEN. However, as in younger patients, renal function must be determined prior to the administration of PEG-INTRON® PEN.

**Use in patients under the age of 18 years:** Safety and effectiveness of PEG-INTRON® PEN in these patients have not been evaluated. PEG-INTRON® PEN is not recommended for use in children and adolescents under the age of 18 (see Indication and Usage).
Preparation and Administration: PEG-INTRON® PEN contains peginterferon alfa-2b powder at strengths of 50, 80, 100, 120 and 150 mcg and the solvent (sterile water for injection) for single disposable use. The powder and solvent are contained in a dual-chamber cartridge. When the cartridge is activated, the powder will be reconstituted with the solvent and up to 0.5 ml of the reconstituted solution will be administered. A small volume is lost during preparation of the reconstituted solution when the dose is measured and injected. Thus, each unit contains an excess amount of solvent and peginterferon alfa-2b powder to ensure delivery of the labeled dose in 0.5 ml in the PEG-INTRON® PEN. The reconstituted solution for each of the above strengths has a concentration of 50, 80, 100, 120 and 150 mcg/0.5 ml. The labeled strength will be contained in 0.5 ml of the reconstituted solution.

PEG-INTRON® PEN is used for subcutaneous administration after the powder is reconstituted as instructed, the injection needle is attached, and the Pre-filled Pen is set for the administration of the prescribed dose. A complete and illustrated set of instructions is provided at the end of this insert.

Remove PEG-INTRON® PEN from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discoloration is present. Discard any unused solution. The PEG-INTRON® PEN product must not be mixed with other injectable products.

Stability of the reconstituted solution: Stability for the reconstituted solution has been demonstrated for 24 hours at 2°C - 8°C. If not used immediately, PEG-INTRON® PEN should be stored in the refrigerator (2°C - 8°C) and used within 24 hours.

INCOMPATIBILITIES: PEG-INTRON® PEN should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also Preparation and Administration).

DRUG INTERACTIONS: No pharmacokinetic interaction were noted between PEG-INTRON® PEN and ribavirin in a multiple-dose pharmacokinetic study.

Results of a single-dose study with PEG-INTRON® PEN demonstrated no effect on the activity of cytochrome P450 isoenzymes CYP1A2, CYP2C8/9, CYP2D6 and CYP3A4 or hepatic N-acetyl transferase. The literature, however, reports up to a 50% reduction in clearance of CYP1A2 substrates (e.g. theophylline) when administered with other forms of interferon alpha and therefore caution should be excercised when PEG-INTRON® PEN is used with medications metabolized by CYP1A2, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

A multiple dose probe study assessing P450 substrates was performed in 26 subjects with chronic hepatitis C, who receive a once-weekly PEG-INTRON® (1.5 mcg/kg) for 4 weeks. There was no inhibition of CYP1A2, 3A4, or N-acetyltransferase. There was a 27% increase in activity of CYP2C8/9 and a 69% increase in CYP2D6. Caution should be used when administering interferon alfa-2b with medications metabolized by CYP2C8/9 and CYP2D6.
Methadone: In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naive to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PEG-INTRON® subcutaneously for 4 weeks increased R-methadone AUC by approximately 15% (95% CI for AUC ratio estimate 103 - 128%). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effects, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HIV/HCV Co-infection

Nucleoside analogs: Ribavirin has been shown in vitro to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these finding 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 viraemia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with ribavirin concurrently with either of these two agents. If HIV RNA levels increase, the use of ribavirin concomitantly with reverse transcriptase inhibitors must be reviewed (see ribavirin product information).

Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides in vitro. This activity could potentiate the risk of lactic acidosis induce by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin product information).

Patients co-infected with the Human Immunodeficiency Virus (HIV) and are receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding treatment with PEG-INTRON® and ribavirin to HAART.

ADVERSE EFFECTS

PEG-INTRON® PEN monotherapy: Most undesirable effects were mild or moderate in severity and not treatment limiting. The majority of patients reported headache and myalgia.

Very commonly reported effects (≥ 10% of patients) were pain/inflammation at injection site, fatigue, rigors, fever, depression, arthralgia, nausea, alopecia, musculoskeletal pain, irritability, influenza-like symptoms, insomnia, diarrhea, abdominal pain, asthenia, pharyngitis, weight decrease, anorexia, anxiety, impaired concentration, dizziness, and injection site reaction.

Commonly reported effects (≥ 2% of patients) were pruritus, dry skin, malaise, increased sweating, right upper quadrant pain, neutropenia, leukopenia, anemia, rash, vomiting, dry mouth, emotional lability, nervousness, dyspnea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthesia, coughing, agitation, sinusitis, hypertonia, hyperesthesia, blurred vision, confusion, flatulence, decrease libido, erythema, eye pain, apathy, hypoesthesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia menstrual disoder.
In patients treated with PEG-INTRON® PEN in clinical trials, severe psychiatric events were uncommon; life-threatening psychiatric events occurred infrequently. These events included suicide, attempted suicide, and suicidal ideation, aggressive behaviour, sometimes directed towards others, and psychosis including hallucinations. Granulocytopenia (<0.75 x 10⁹/l) occurred in 4% and 7%, and thrombocytopenia (<70 x 10⁹/l) in 1% and 3%, respectively in patients receiving 0.5 or 1.0 micrograms/kg of PEG-INTRON® PEN. Very rarely sarcoidosis or exacerbation of sarcoidosis has been reported.

**PEG-INTRON® PEN in combination with ribavirin:** In addition to the adverse effects reported with PEG-INTRON® PEN Monotherapy, the following adverse effects have been reported with PEG-INTRON® PEN in combination with ribavirin:

Adverse effects reported between 5% and 10% in the treatment group receiving the recommended dose of PEG-INTRON® + Ribavirin were increased sweating, chest pain, right upper quadrant (RUQ) pain, paresthesia, hypothyroidism, constipation, dyspepsia, tachycardia, agitation, nervousness, menorrhagia, menstrual disorder, non productive cough, rhinitis, taste perversion and burred vission.

Adverse effects reported between 2% and 5% in the treatment group receiving the recommended dose of PEG-INTRON® + Ribavirin were injection site pain, flushing, hypotension, lacrimal gland disorder, erythema, malaise, hypertension, syncope, confusion, hyperesthesia, hypoesthesia, hypertonia, decrease libido, tremor, vertigo, hyperthyroidism, flatulence, gingival bleeding, glossitis, loose stools, stomatitis, ulcerative stomatitis, hearing impairment/loss, tinnitus, palpitation, thirst, thrombocytopenia, aggressive behaviour, somnolence, herpes simplex, fungal infection, amenorrhea, prostatitis, otitis media, bronchitis, nasal congestion, respiratory disorder, rhinorrhea, sinusitis, eczema, abnormal hair texture, photosensitivity reaction, erythematous rash, maculopapular rash, migraine, conjunctivitis, and lymphadenopathy.

Rarely reported events with interferon alfa-2b include seizures, pancreatitis, hypertriglyceridemia, arrhythmia, diabetes and peripheral neuropathy.

Very rarely alfa interferons, including PegIntron, used alone or in combination with ribavirin may be associated with aplastic anemia or pure red cell aplasia.

**Other reported adverse effects that may be occur in association with PEG-INTRON® PEN in combination with ribavirin:**

Other ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular edema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilledema (see PRECAUTIONS). Cardiovascular (CVS) adverse reactions, particularly arrhythmia appeared to be correlated mostly with pre-existing CVS disease and prior cardiotoxic therapy, Cardiomyopathy that may be reversible upon discontinuation of interferon alfa has been reported rarely in patients without prior evidence of cardiac disease.

A wide variety of autoimmune and immune mediated disorder have been reported with alpha
interferons including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura.

Following the marketing of peg-interferon alfa-2b, rhabdomyolysis, myositis, renal insufficiency and renal failure have been reported rarely. Cardiac ischemia, myocardial infarction, cerebrovascular ischemia, cerebrovascular hemorrhage, encephalopathy (see PRECAUTIONS) ulcerative and ischemic colitis, sarcoidosis or exacerbation of sarcoidosis, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, and injection site necrosis also have been reported very rarely.

HIV/HCV Co-infected patients
Treatment with peginterferon alfa-2b in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4 + cell percentage. The decrease in CD4 + cell counts was reversible upon dose reduction or cessation of therapy. The use of peginterferon alfa-2b in combination with ribavirin had no observable negative impact on the control of HIV viremia during therapy or follow-up. Limited safety data (N=25) are available in co-infected patients with CD4 + cell counts <200/µl.

Table 9 summaries the safety of PEG-INTRON® in combination with ribavirin for HIV/HCV co-infected patients.

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2b/ribavirin n=194</td>
<td>Interferon alfa-2b/ribavirin n=189</td>
</tr>
<tr>
<td>Peginterferon alfa-2b/ribavirin n=52</td>
<td>Interferon alfa-2b/ribavirin n=43</td>
</tr>
<tr>
<td><strong>Treatment Discontinuation</strong></td>
<td></td>
</tr>
<tr>
<td>All reasons</td>
<td>76 (39%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>33 (17%)</td>
</tr>
<tr>
<td><strong>Dose Modification</strong></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>54 (28%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>19 (10%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (5%)</td>
</tr>
</tbody>
</table>

For HIV/HCV co-infected patients receiving peginterferon alfa-2b in combination with ribavirin, other undesirable effects which have been reported in the larger study (Study 1): neutropenia (26%), lipodystrophy acquired (13%), CD4 lymphocytes decreased (8%), appetite decreased (8%), gamma-glutamyltransferase increased (9%), back pain (5%), rhinitis (5%), blood amylase
increased (6%), blood lactic acid increased (5%), cytolytic hepatitis (6%), paraesthesia (5%), lipase increased (6%).

**Laboratory values for HIV/HCV co-infected patients**
Although hematological toxicities of neutropenia, thrombocytopenia and anemia occurred more frequently in HIV/HCV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment. In the larger study (Study 1), decrease in absolute neutrophil count levels below 500 cells/mm³ was observed in 4% (8/194) of patients and decrease in platelets below 50,000/mm³ was observed in 4% (8/194) of patients receiving peginterferon alfa-2b in combination with ribavirin. Anemia (hemoglobin <9.4g/dl) was reported in 12% (23/194) of patients treated with peginterferon alfa-2b in combination with ribavirin.

Please refer to the respective product information of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PEG-INTRON® in combination with ribavirin.

**CONTRAINDICATIONS:**
- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women. PEG-INTRON® PEN in combination with ribavirin must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy;
- Women who are breast feeding
- Existence of or a history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months;
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute
- Auto immune hepatitis or a history of auto immune disease
- Severe hepatic dysfunction or decompensated cirrhosis of the liver
- Pre-existing thyroid disease unless it can be controlled with conventional treatment
- Epilepsy and/or compromised central nervous system (CNS) function
- Men whose female partners are pregnant (if PEG-INTRON® PEN treatment is used in combination with ribavirin).
- Decompensated liver disease or severe renal dysfunction (creatinine clearance < 50ml/min).
- When used in combination with ribavirin, patients with creatinine clearance < 50ml/min.

**PRECAUTIONS:**
**Psychiatric and Central Nervous System (CNS):** Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PEG-INTRON® PEN. Other CNS effects including confusion and alterations of mental status have been observed with alpha interferon. More significant obtundation and coma including cases of encephalopathy, have been observed in some patients, usually elderly, treated with higher doses
of interferon alfa-2b. While these effects are generally reversible, in a few patients full resolution too up to three weeks. Very rarely, seizures have occurred with high doses of PEG-INTRON® PEN. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PEG-INTRON® PEN.

Patients with existence of, or history of severe psychiatric conditions: if treatment with peginterferon alfa-2b is judge necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of psychiatric condition.

Cardiovascular system: As with interferon alpha, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders receiving therapy with PEG-INTRON® PEN therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primaly supraventricular) usually respond to conventional therapy but may require discontinuation of PEG-INTRON® PEN.

Acute hypersensitivity: Acute hypersensitivity reaction, (e.g. urticaria, angioedema, bronchoconstriction, anaphylaxis), have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PEG-INTRON® PEN, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: As with treatment with any interferon, discontinue treatment with PEG-INTRON® PEN in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Renal function: Patients with impairment of renal function should be closely monitored for signs and symptoms of toxicity. PEG-INTRON® should not be used in patients with chronic renal failure or creatinine clearance < 50 ml/min.

Fever: While fever may be associated with the flu like syndrome reported commonly during any interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing therapy with PEG-INTRON® PEN since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely. If appropriate, discontinue PEG-INTRON® treatment. Prompt discontinuation of therapy and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.
**Autoimmune disease:** The development of autoantibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

**Ocular changes:** Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of ocular symptoms, including of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PEG-INTRON® PEN is recommended in patients with diabetes mellitus or hypertension. Discontinuation of PEG-INTRON® PEN should be considered in patients who develop new or worsening ophthalmological disorders.

**Thyroid changes:** Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PEG-INTRON® PEN may be continued if TSH levels can be maintained in the normal range by medication.

**Metabolic disturbances:** Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

**HCV/HIV Co-infection:**

**Mitochondrial toxicity and lactic acidosis:**
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PEG-INTRON® and ribavirin to HAART therapy.

**Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:**
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensations should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

**Haematological abnormalities in HCV/HIV co-infected patients:**
HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patient. Patients treated with PEG-INTRON® and ribavirin combination therapy and zidovudine are at increased risk developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended.

Patients with low CD4 counts:
In patients co-infected with HCV/HIV, limited efficacy and safety data (N=25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts. Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PEG-INTRON® and ribavirin.

**Dental and periodontal disorders:**
Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PEG-INTRON® and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PEG-INTRON® and ribavirin. Patients should brush their teeth thoroughly twice daily and have regularly dental examinations. In addition some patients may experience vomiting. If the reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

**Organ transplant recipients:**
The safety and efficacy of PEG-INTRON® alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

**Other:** Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PEG-INTRON® treatment in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

**Laboratory test:** Standard haemologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PEG-INTRON® treatment are:

- Platelets $\geq 100,000/\text{mm}^3$
- Neutrophil count $\geq 1,500/\text{mm}^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

**Effects on ability to drive and use machines:** Patients who develop fatigue, somnolence or confusion during treatment with PEG-INTRON® PEN are cautioned to avoid driving or operating machinery.

**USAGE DURING PREGNANCY AND LACTATION:**
**MONOTHERAPY:**
Interferon alfa-2b has been shown to be abortifacient in primates. PEG-INTRON® PEN is likely to also cause this effect. Because there are no data on the use of PEG-INTRON® PEN in pregnant women, PEG-INTRON® PEN is not recommended for use during pregnancy.
PEG-INTRON® PEN is recommended for use in fertile women only when they are using effective contraception during treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue the treatment or discontinue nursing, taking into account the importance of the medicinal product to the mother.

**COMBINATION THERAPY:**

PEG-INTRON® PEN with ribavirin must not be used during pregnancy. Significant teratogenic and/or embryocidal potential have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses as low as one twentieth of the recommended human dose. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the ribavirin dose. Survival of fetuses and offspring was reduced.

*Female patients:* Ribavirin capsules must not be used by women who are pregnant (see Contraindications). Extreme care must be taken to avoid pregnancy in female patients. Therapy with Ribavirin capsules must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and their partners must each use an effective contraceptive during treatment and for six months after treatment has been concluded; 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 fetus.

*Male patients and their female partners:* Extreme care must be taken to avoid pregnancy in partners of male patients taking ribavirin. Ribavirin accumulates intracellularly 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 ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Male patients and their female partners of childbearing age must, therefore, be counseled to each use an effective contraceptive during treatment with ribavirin and for six months after treatment has been concluded. PEG-INTRON® PEN in combination with ribavirin is recommended for use in fertile women only when they are using effective contraception during the treatment period.

*Lactation:* It is not known whether PEG-INTRON® PEN in combination with ribavirin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

**OVER DOSAGE INFORMATION:**

Doses up to 10.5 times the intended dose have been reported in hepatitis patients. The maximum daily dose reported is 1200 mcg/day for one day. In general, the adverse events seen in overdose cases involving Trademark are consistent with the known safety profile for PEG-
INTRON®; however, the severity of the events may be increased. No specific antidote for PEG-INTRON® is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control center (PCC).

**STORAGE:** Store at 2°C to 8°C

**PRESENTATION**
- PEG-INTRON® PEN 50 mcg, box of 1 pen/0.5ml; Reg. No. DKI0687101344A1
- PEG-INTRON® PEN 50 mcg, box of 4 pen @ 0.5ml; Reg. No. DKI0687101344A1
- PEG-INTRON® PEN 80 mcg, box of 1 pen/0.5ml; Reg. No. DKI0687101344B1
- PEG-INTRON® PEN 80 mcg, box of 4 pen @ 0.5ml; Reg. No. DKI0687101344B1
- PEG-INTRON® PEN 100 mcg, box of 1 pen/0.5ml; Reg. No. DKI0687101344C1
- PEG-INTRON® PEN 100 mcg, box of 4 pen @ 0.5ml; Reg. No. DKI0687101344C1
- PEG-INTRON® PEN 120 mcg, box of 1 pen/0.5ml; Reg. No. DKI0687101344D1
- PEG-INTRON® PEN 120 mcg, box of 4 pen @ 0.5ml; Reg. No. DKI0687101344D1
- PEG-INTRON® PEN 150 mcg, box of 1 pen/0.5ml; Reg. No. DKI0687101344E1
- PEG-INTRON® PEN 150 mcg, box of 1 pen @ 0.5ml; Reg. No. DKI0687101344E1

**ON MEDICAL PRESCRIPTION ONLY**
**HARUS DENGAN RESEP DOKTER**

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