

## FDA Approves Schering's Application to Unbundle Rebetron

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On July 26, 2001 the Federal Food and Drug Administration (FDA) approved the unbundling of Schering's Rebetron package of Intron A (interferon) and Rebetol (ribavirin). This approval will allow the dispensing of ribavirin separately for use with other interferons. Furthermore, this action will permit doctors to prescribe ribavirin off-label for use with the newly FDA approved Peg-Intron, a form of time-released interferon.

The FDA approval to market Rebetol separately will require Schering to include product labeling that Rebetol (ribavirin) alone is ineffective for treatment of hepatitis C and should not be used as a stand-alone treatment. Product labeling will also require information on possible side effects such as fatigue, muscle and joint pain. Additionally, it will be noted that the anemia produced by ribavirin can exacerbate heart disease that could be fatal. Ribavirin can also cause birth defects and birth control by both partners should be practiced during and for six months after patients stop taking it.

The issue of bundling has a long history that dates back to 1998 when the FDA approved the marketing of the combination of Intron A (Schering's interferon) and Rebetol (Schering's ribavirin). The marketing approval of the combination marketing is unprecedented and has angered many healthcare advocates who fear the same bundling practices will be applied to other medications. HCV community activists were angered because it did not allow for prescribing of ribavirin with other interferons, notably Amgen's Infergen and Roche's Roferon. As well, the bundling did not allow dose adjustments of ribavirin that may be needed for patient safety and/or drug effectiveness. Furthermore, the HCV community and healthcare advocates were outraged by the high cost of combination treatment, which is approximately \$18000/yr. Even more disturbing for many is the belief that the bundled product has hindered research for more effective HCV treatments because it made ribavirin basically unavailable and/or cost prohibitive.

Community activists, among them, Mr. Brian Klein of Hepatitis C Action and Advocacy (HAAC) fought with Schering and the FDA to unbundle Rebetron and lower the cost. As a result of community pressure, the FDA issued a statement that they would look favorably upon Schering to submit an application to unbundle the products. However, even with pressure from the FDA, community activists and some doctors, Schering would not consider unbundling, citing safety concerns with the use of ribavirin with other interferons. Community advocates challenged this issue since safety concerns have not surfaced in Europe where the two medications are sold separately.

But a new wrinkle appeared – compounding pharmacies. Due to the awareness brought about by community activists and a loophole in the law, compounding pharmacies were allowed to prescribe ribavirin capsules separately. Led by Fischer Pharmacy, compounded ribavirin allowed doctors to prescribe ribavirin separately with the added benefit --- a 75% cost reduction in ribavirin compared to the price charged by Schering.

According to a company press release, Rebetol will be available separately sometime this fall. "While I applaud the unbundling of Retebron, I suspect that Schering is likely to market Rebetol (ribavirin) at an exorbitant price" states Mr. Brian Klein, founding member of HAAC. "We expect Schering to charge as much as \$800 – 1,000 for a month's supply." Additionally, Klein believes the pricing of Rebetol is an attempt by Schering to discourage its off label use and is a strategy for future marketing for the PEG-Intron and Rebetol, which is expected to be approved by the FDA sometime in August, 2001.

The financial stakes have been enormous. Schering has cornered the hepatitis C treatment market with revenues in the billions of dollars. Future profits are expected to be even higher with the pending approval of the combination of pegylated interferon and ribavirin. There are two pegylated products – Schering's PEG-Intron and Roche's Pegasys. At the beginning of 2001, the FDA approved the marketing of PEG-Intron, a time released interferon that has been shown in clinical trials to be superior to standard interferon. Roche's

Pegasys is pending FDA approval. Additionally, clinical trial data on the combination of pegylated interferon and ribavirin increases the rate that the body is able to permanently clear the hepatitis C virus to undetectable levels in up to 54-56% of individuals treated.

To further complicate the issue, Schering's exclusivity for ribavirin will expire at the end of this year. This means that ribavirin will be available for sale as a generic medication at a substantially reduced cost. Community advocates suspect that the unbundling is just a ploy by Schering to block the approval of a generic ribavirin. They also believe that once a company applies to the FDA to market generic ribavirin, that Schering will sue the generic maker for patent infringement. This action would require the FDA to delay marketing approval of the generic ribavirin license for up to 30 months and could possibly guarantee Schering exclusivity in the market place for pegylated interferon and ribavirin.

The controversy of ribavirin will continue to unfold within the next couple of months. Speculation will give way to more concrete information and actions by both Schering and HCV advocates. Stay Tuned!