



# HCSP FACT SHEET

HCV ADVOCATE

• HCV TREATMENT: FDA-APPROVED MEDICATIONS •

## Interferon, Ribavirin & HCV Protease Inhibitors

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### Foreword

There are three different types of drugs that are approved to treat chronic hepatitis C—interferon including pegylated interferon, ribavirin and HCV protease inhibitors. Interferon has been the backbone of HCV therapy since 1991; ribavirin has been used in combination with an interferon since 1998 and HCV protease inhibitors have been used in combination with interferon and ribavirin since 2011. Treatment success with interferon monotherapy was minimal, but when ribavirin was added to interferon therapy the treatment success rates dramatically improved for all genotypes. The approval and inclusion of an HCV protease inhibitor to interferon and ribavirin therapy for the treatment of chronic HCV genotype 1 pushed the cure rates up to 79%.

Interferon (in one form or another) has been used to treat hepatitis C since 1991 and ribavirin has been used in combination with an interferon product since 1998.

**There are 3 types of Interferons** that are used to treat hepatitis C—Type II and PEG-IFN-lambda. The third interferon is a type I interferon that has not been approved to treat hepatitis C. Interferons are naturally produced by the body usually in response to an infection.

- Type I interferon is mainly involved with controlling the immune functions of the body.
- PEG-IFN-lambda, is a protein that produced by the body in response to an infection.
- There is only one form of Type II interferon – gamma interferon.

**Type I** interferon is known as alpha or beta and is made up of proteins produced by the body in response to a viral infection. For instance, when someone becomes infected with the flu virus the immune system immediately produces and releases various types of interferon to protect cells from the invading virus. The symptoms people experience from the flu, such as

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*A publication of the  
Hepatitis C Support Project*

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The information in this fact sheet is designed to help you understand and manage HCV and is not intended as medical advice. All persons with HCV should consult a medical practitioner for diagnosis and treatment of HCV.

This information is provided by the Hepatitis C Support Project a nonprofit organization for HCV education, support and advocacy

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### HCV – Interferon, Ribavirin & HCV Protease Inhibitors

muscle pain, fever and headaches, are due to the body's natural production of interferon.

In more detail, interferon works by binding to cell surface receptors and triggering the production of intracellular second messengers, including 2'5' oligo-adenylate synthetase, protein kinases, cell surface proteins, and nuclear proteins.

Interferon also works in other ways by increasing the body's immune response against viruses and infected cells:

- **Antiviral action** – Interferon helps to prevent the entry of a virus into a cell, which limits the replication of new viruses and the amount of new cells that the virus infects. Within the liver cell interferon inhibits the replication of viruses by preventing the virus from uncoating and by interfering with viral protein synthesis.
- **Immunomodulatory effect** – Interferon stimulates the production of cytokines (chemical messengers) that activate macrophages, natural killer (NK) cells, and cytotoxic T-lymphocytes (CTLs, or killer T-cells) which then surround and kill the infected cell and the virus within the cell.
- **Antitumor effects** – Interferon reduces the production of both normal and malignant (cancerous) cells and inhibits oncogene expression. Interferon also enhances direct T-cell-mediated cytotoxicity against tumor cells. This kills cancer and tumor cells.
- **Enhanced cell surface expression of MHC** – Interferon enhances the expression of class 1 major histocompatibility (MHC) antigens on the surface of infected cells. Expression of these proteins on the cell surface allows virus-infected cells to be targeted and destroyed by CTLs.

Sometimes the body does not make enough natural interferon to effectively fight an infection – the addition of genetically re-engineered interferon helps the body to fight off a viral infection such as hepatitis C.

#### **Standard Interferon**

Standard interferons (also called conventional interferon) are administered by subcutaneous injection (right underneath the skin) three times a week. Standard interferon's half life (the time required by the body to metabolize or inactivate half the amount of the substance) is two to five hours. Because of standard interferon's short half-life it is unable to constantly suppress the hepatitis C virus. Standard interferon is a pre-mixed solution. The first standard interferon, Intron A brand, was approved in 1991.

The most common FDA approved standard interferons used to treat hepatitis C include Genentech's Roferon-A, Merck's Intron A, and Kadmon's Infergen.

#### **Pegylated Interferon**

Pegylated interferon is a long-acting formulation of interferon that can be injected less often – once a week. Pegylation is a process in which polyethylene glycol (the PEG molecule) is attached to a protein. This creates a shield around the interferon which helps to protect it and also delays the breakdown and clearance of interferon from the body. Since the PEG module allows interferon to stay in the body longer there is greater suppression of the hepatitis C virus.

There are currently two FDA approved pegylated interferons – Merck's Peg-Intron was approved in August 2001; and Roche's Pegasys was approved in October 2002.

**HCV – Interferon, Ribavirin & HCV Protease Inhibitors**

**Interferons in Development**

There are many other types of interferon that are being developed and tested to treat hepatitis C.

**IL-29** (type III interferon), also known as lambda interferon is in phase II studies for the treatment of HCV in combination with different types of HCV protease, NS5A inhibitors and ribavirin. Preliminary data suggest that this type of once-a-week dose of interferon may have similar efficacy, but a lower side effect profile than pegylated interferon. **Belerofon** (an oral medication), and **Locteron** look promising.

**Ribavirin**

Ribavirin (Rebetol, produced by Merck; Copegus, produced by Genentech; or Ribasphere, produced by Kadmon Pharmaceuticals) is a nucleoside analog (also called a nucleoside reverse transcriptase inhibitor, or NRTI) antiviral drug. It is taken orally (by mouth) twice a day. The exact way ribavirin works is unknown. However, it is believed that when ribavirin enters a cell it is phosphorylated; it then acts as an inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH). IMPDH inhibitors such as ribavirin reduce the intracellular synthesis and storage of guanine, a nucleotide "building block" necessary for DNA and RNA production, thus inhibiting viral replication. IMPDH inhibitors also interfere with the reproduction of rapidly proliferating cells and cells with a high rate of protein turnover; because of this, IMPDH inhibitors can cause side effects such as nausea and immunosuppression.

Treatment with ribavirin monotherapy has little effect on HCV RNA levels, but is associated with a decline in serum ALT. This suggests that ribavirin may not be acting as an antiviral agent, but rather as a modulator of immune system function. Since ribavirin monotherapy for HCV is ineffective, it is only approved for use in combination with FDA approved interferons.

To increase the absorption of ribavirin it should be taken with food.

**HCV Protease Inhibitors**

HCV protease inhibitors work by preventing the hepatitis C virus from binding to the site that the virus' protease enzymes use to replicate. Currently, Merck's Victrelis (boceprevir) and Vertex's Incivek (telaprevir) are approved by the Food and Drug Administration to treat HCV genotype 1 patients. Victrelis and Incivek are combined with pegylated interferon and ribavirin. The treatment duration depends on how quickly or slowly the HCV medications work (response-guided therapy)—24, 36 or 48 weeks. Victrelis and Incivek are taken every 7 to 9 hours. Victrelis and Incivek must be used with pegylated interferon and ribavirin due to the high rate of drug resistance when used as a monotherapy.

Victrelis should be taken with a meal or light snack; Incivek should be taken with food that is not low fat (1/2 cup nuts; 3 tablespoons of peanut butter, etc.).

**HCV Protease Inhibitors in Development**

There are four HCV inhibitors in separate Phase III studies:

- TMC425 (Tibotec) protease inhibitor (HCV genotype 1)
- BI 201335 (Boehringer-Ingelheim) protease inhibitor (HCV genotype 1),
- BM-790052 (NS5A inhibitor) HCV genotype 1, and
- PSI-7977 (polymerase inhibitor) HCV genotype 1

In the above studies, the inhibitors are taken QD (once a day) in combination with pegylated interferon plus ribavirin for 12, 24 or 48 weeks.

### HCV – Interferon, Ribavirin & HCV Protease Inhibitors

In addition, there are studies underway that will combine different types of HCV inhibitors with and without interferon and ribavirin.

#### Today's Standard of Care:

The current standard of care by genotype is listed below:

- Genotype 1: a combination of pegylated interferon, ribavirin and an HCV protease inhibitor (boceprevir or telaprevir). The standard duration of treatment is a total of 24, 36 or 48 weeks.
  - Pegylated interferon is a subcutaneous injection—once weekly.
  - Ribavirin is a pill. The dose is based on body weight (1,000/1,200mg) and divided into two equal doses twice a day.
  - HCV protease inhibitor (boceprevir or telaprevir) is taken every 7 to 9 hours with food – boceprevir can be taken with a snack or meal; telaprevir is taken with food that is not low-fat.
- Genotypes 2 and 3: a combination of pegylated interferon and ribavirin taken for 24 weeks.
  - Pegylated interferon is a subcutaneous injection—once weekly.
  - Ribavirin is a pill. The dose is given 800mg daily—dose is divided into two equal doses. Ribavirin is taken with food.

#### HCV Treatment Response Rates\*

##### Genotype 1:

- Incivek (telaprevir), pegylated interferon plus ribavirin-Incivek (750 mg) is a pill that is taken every 7 to 9 hours, pegylated interferon is a weekly injection and ribavirin is a pill taken twice a day.
  - Treatment Naïve: Up to 79% SVR\*\*

- Treatment Experienced ( relapsers, partial responders, null responders): Up to 86% SVR

Treatment duration based on response-guided therapy: 24 or 48 weeks

- Victrelis (boceprevir), pegylated interferon plus ribavirin—Victrelis (800 mg) is a pill that is taken every 7 to 9 hours, pegylated interferon is a weekly injection and ribavirin is a pill taken twice a day.
  - Treatment Naïve: Up to 66% SVR
  - Treatment experienced (including relapsers, partial responder—null responders were not included) : up to 66%

Treatment duration based on response guided therapy: 24, 36 or 48 weeks (included 4-week lead-in of pegylated interferon plus ribavirin)

##### Genotypes 2 – 6:

- Pegasys plus Copegus (Genentech (Member of the Roche Group))
  - Genotypes 2 – 6: 70% SVR (48 weeks /1000-1200 mg ribavirin)
  - Genotypes 2 & 3: 82% SVR (24 weeks/800 mg ribavirin)
- PEG-Intron plus Rebetol (Merck (includes Schering-Plough subsidiary))
  - Genotypes 2 - 6: 75% SVR (48 weeks/800 mg ribavirin)

**\*Note:** These are averages for all HCV patients. Response rates vary for certain groups of people. All figures taken from the manufacturers' package inserts.

\*\* SVR means sustained viral response. This means that HCV remains undetectable for at least six months after treatment is completed.

**HCV – Interferon, Ribavirin & HCV Protease Inhibitors**

Drug/Brand	Type	Year Approved	Comments
Ribavirin(RBV)	Nucleoside analog	1998	Must be taken with interferon
Pegylated Interferon Alpha 2b (PegIntron)	Interferon	2001	Taken with RBV/PI
Pegylated interferon Alpha 2 a (Pegasys)	Interferon	2002	Taken with RBV/PI
Telaprevir (Incivek)	HCV Protease Inhibitor (PI)	2011	Taken with INF/RBV
Boceprevir (Victrelis)	HCV Protease inhibitor (PI)	2011	Taken with INF/RBV

*Related publications:*

- **Incivek (telaprevir)**  
[www.hcvadvocate.org/hepatitis/factsheets\\_pdf/Incivek.pdf](http://www.hcvadvocate.org/hepatitis/factsheets_pdf/Incivek.pdf)
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*For more information*

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