

# Hepatitis C treatment factsheet

## *Zepatier* (grazoprevir + elbasvir)

*Zepatier* is a new medication used to treat hepatitis C. It is a combination pill containing grazoprevir plus elbasvir. It was approved in Europe in July 2016 for treatment of adults with genotype 1 or 4 chronic hepatitis C.

*Zepatier* offers a new interferon-free option for many people with hepatitis C. Some people with harder-to-treat disease may do better if they take *Zepatier* with ribavirin. Successful treatment reduces the risk of long-term complications of hepatitis C such as cirrhosis, liver cancer or needing a liver transplant.

### How does *Zepatier* work?

*Zepatier* contains two direct-acting antiviral drugs that target different steps of the hepatitis C virus (HCV) lifecycle. Grazoprevir is an HCV protease inhibitor, meaning it interferes with the protease enzyme which the virus needs to reproduce. Elbasvir is an HCV NS5A replication complex inhibitor that interferes with another protein HCV uses to reproduce. Targeting two different steps of the HCV lifecycle makes it harder for the virus to develop drug resistance.

### Who can use *Zepatier*?

*Zepatier* is approved for use by adults with chronic hepatitis C, meaning infection lasting more than six months. It is approved for people with HCV genotypes 1 or 4. Genotype 1 is the most common type in Europe. People with genotype 1a should receive a test for virus mutations that can cause drug resistance before starting *Zepatier*.

*Zepatier* can be used by people being treated for hepatitis C for the first time and for retreatment of people who were not cured with previous interferon-based therapy (known as 'treatment-experienced').

*Zepatier* has been tested in people with HIV and HCV co-infection. Response rates and side-effects were similar to those seen in HIV-negative people, but *Zepatier* should not be used with certain HIV medications. People with HIV and HCV co-infection who want to take *Zepatier* should do so under the care of a doctor who has experience treating both infections.

*Zepatier* can be used by people with compensated cirrhosis who still have relatively good liver function. It is not recommended for people with moderate or severe liver impairment or decompensated cirrhosis (Child-Pugh class B or C). It has not yet been tested for people who are awaiting or have received a liver transplant.

*Zepatier* can be used by people with chronic kidney disease and those undergoing kidney dialysis.

### How is *Zepatier* taken?

*Zepatier* is taken as a single pill once daily with or without food. Some people will also need to take ribavirin pills twice daily, with doses based on body weight. The length of treatment and whether *Zepatier* should be taken with ribavirin depends on HCV genotype and prior treatment history.

Most people who have not taken HCV treatment before and who have HCV genotype 1 or 4, with or without liver cirrhosis, will be able to take *Zepatier* without ribavirin for 12 weeks.

People with HCV genotype 1a, which is harder to treat than 1b, should first receive a test for HCV NS5A mutations – also known as polymorphisms or resistance-associated variants (RAVs) – that can cause resistance to elbasvir and make *Zepatier* less effective. People with these mutations should add ribavirin and extend treatment to 16 weeks.

People with genotype 1a without these mutations and those with genotype 1b who were previously unsuccessfully treated with pegylated interferon and ribavirin (abbreviated as 'IFN/RBV' in the table below) can take *Zepatier* alone for 12 weeks.

People with genotype 1a or 1b who were treated with pegylated interferon and ribavirin plus the older HCV protease inhibitors boceprevir (*Victrelis*), telaprevir (*Incivo*) or simeprevir (*Olysio*) should add ribavirin. Previously treated people with genotype 4 should both add ribavirin and extend treatment to 16 weeks.

	Treatment regimen	Length of treatment
<b>Genotype 1a</b> Previously untreated or IFN/BV-experienced without NS5A polymorphisms	<i>Zepatier</i>	12 weeks
<b>Genotype 1a</b> Previously untreated or IFN/RBV-experienced with NS5A polymorphisms	<i>Zepatier</i> + ribavirin	16 weeks
<b>Genotype 1b</b> Previously untreated or IFN/RBV experienced	<i>Zepatier</i>	12 weeks

	Treatment regimen	Length of treatment
<b>Genotype 1a or 1b</b> Prior IFN/RBV and protease inhibitor treatment	<i>Zepatier</i> + ribavirin	12 weeks
<b>Genotype 4</b> Previously untreated	<i>Zepatier</i>	12 weeks
<b>Genotype 4</b> IFN/RBV-experienced	<i>Zepatier</i>	16 weeks

Recommended *Zepatier* uses for people with HIV and HCV co-infection are the same as those for HIV-negative people. However, it should not be used with antiretroviral medications that can interact with *Zepatier*, including HIV protease inhibitors, efavirenz (*Sustiva*) or regimens that contain ritonavir or cobicistat as ‘boosters’.

*Zepatier* is not approved for people with HCV genotypes 2, 3, 5 or 6.

## How effective is *Zepatier*?

*Zepatier* works better for some people than for others.

People with higher HCV viral load, or HCV NS5A mutations – also known as polymorphisms or resistance-associated variants (RAVs) – that can cause resistance to elbasvir, have a lower chance of cure. This may be overcome by longer treatment or by adding ribavirin, which helps prevent viral relapse.

Unlike some other direct-acting antivirals, having more advanced liver disease, including early cirrhosis, does not appear to have much effect on response to *Zepatier*. However, *Zepatier* is not suitable for use in advanced cirrhosis (Child-Pugh B or C).

Other factors that traditionally predict poor response to interferon-based therapy do not make as much difference with interferon-free treatment.

## *Zepatier* treatment response

People with sustained virological response, who still have undetectable HCV viral load 12 weeks after finishing treatment (known as ‘SVR12’), are considered cured.

The safety and effectiveness of *Zepatier* were tested in nearly 1400 people with chronic hepatitis C in several clinical trials. Overall, 90 to 100% of study participants with HCV genotype 1 or 4 were cured using *Zepatier* with or without ribavirin.

*Zepatier* alone for 12 weeks cured 95% of previously untreated people with HCV genotype 1, with or without cirrhosis, in the phase 3 C-EDGE treatment-naïve study, and cured HCV for 96% of people with genotype 1 HCV and HIV co-infection in the C-EDGE co-infection trial.

In the C-EDGE treatment-experienced study, 92% of genotype 1 prior non-responders to pegylated interferon and ribavirin were cured using *Zepatier* alone for 12 weeks, rising to 97% using *Zepatier* plus ribavirin for 16 weeks. This study included people with and without cirrhosis and both HIV-negative and HIV-positive people.

The C-SALVAGE study showed that *Zepatier* plus ribavirin for 12 weeks cured 96% of people with or without cirrhosis who had previously been unsuccessfully treated with interferon and ribavirin plus older HCV protease inhibitors.

In the C-SURFER trial, 94% of hepatitis C patients with severe kidney impairment using *Zepatier* alone for 12 weeks were cured. The study included both previously untreated and treatment-experienced people.

For previously untreated people with HCV genotype 4, the combined cure rate using *Zepatier* alone for 12 weeks was 97% in three studies, again including patients with cirrhosis and HIV-positive participants. The response rate was 100% for the small number of people with genotype 4 HCV who used *Zepatier* plus ribavirin for 16 weeks in the C-EDGE treatment-experienced trial.

In the C-EDGE CO-STAR study, *Zepatier* alone for 12 weeks cured HCV for 92% of people who inject drugs who were using opioid substitution therapy such as methadone.

The effectiveness of *Zepatier* in ‘real world’ use may be somewhat lower than cure rates seen in clinical trials, in part because patients may be sicker or have other conditions that make treatment more complicated. It is currently unknown how effective *Zepatier* is in patients who have previously taken treatment with newer direct-acting antivirals.

## What are the side-effects of *Zepatier*?

The drugs in *Zepatier* are generally safe and well tolerated. The most common side-effects seen in clinical trials were fatigue, headache and nausea. A small number of study participants developed elevated levels of the liver enzyme ALT because of grazoprevir. If there are high ALT elevations and/or other signs of possible liver toxicity such as nausea, yellow eyes or skin, patients should urgently consult with their doctors. Ribavirin can cause other side-effects including anaemia (low haemoglobin level).

*Zepatier* has not yet been tested in pregnant or breastfeeding women. Ribavirin can cause birth defects, so it should not be used by pregnant women or their male partners.

## Does *Zepatier* interact with other drugs?

The drugs in *Zepatier* can interact with other drugs that are processed by the same enzymes in the liver or intestines. This can lead to low drug levels that are less effective or high levels that can cause worse side-effects.

Drugs that can interact with *Zepatier* include some antiretroviral drugs (such as HIV protease inhibitors and efavirenz), antibiotics, TB medications, statins and herbal products containing St John's wort. Sometimes drug doses can be adjusted to overcome these interactions, but some medications should not be used together with *Zepatier*. Information about specific drug interactions is available online at [www.hep-druginteractions.org](http://www.hep-druginteractions.org).

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## How can I get *Zepatier*?

*Zepatier* is available by prescription in European Union countries to treat people with hepatitis C genotypes 1 or 4, subject to national funding arrangements. When to start treatment will depend on a number of factors including severity of liver damage (as determined by *FibroScan* or a liver biopsy). Ask your doctor or liver specialist if *Zepatier* may be a good option for you.

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This information is intended to support, rather than replace, consultation with a healthcare professional. Talk to your doctor or another member of your healthcare team for advice tailored to your situation.

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