NHS FIFE

Community Pharmacy Supply for Hepatitis C

Pharmaceutical Care Information Pack

Introduction to Hepatitis C Infection

Chronic hepatitis C constitutes a major global health concern as it is a leading cause of chronic liver disease, cirrhosis and hepatocellular carcinoma. The goal of therapy is to prevent these complications through viral eradication.

The hepatitis C virus (HCV) was first identified in 1989 and HCV infection has become a major health problem worldwide. Approximately 0.8% of the Scottish population is thought to be chronically infected with HCV (around 37,500 individuals). The prevalence of infection varies between population groups ranging from 50% in injecting drug users (IDU) to less than 0.04% among new blood donors.

Up to 80% of patients infected with HCV become chronically infected and most of these patients will show evidence of chronic hepatitis.

Hepatitis C is usually slowly progressive over a period of many years. Five to fifteen per cent of patients with chronic hepatitis may progress to liver cirrhosis over 20 years. Four to nine per cent of patients with cirrhosis will develop liver failure; and two to five per cent of patients with cirrhosis will develop primary hepatocellular carcinoma.

In the UK the two major routes of transmission of HCV have been sharing of drug injecting equipment by IDU and transfusion of infected blood or blood products. Virus inactivation treatment of blood products began in 1987 and since 1991, blood donations have been screened for hepatitis C, eliminating blood products as a source of HCV infection. HCV infection can be effectively treated with combination drug therapy also know as directly-acting antivirals (DAAs) with Sustained Viral Response (SVR) rates in >90% of patients.

Genotypes

HCV is characterised by genotypes and subgroups with prevalence varying depending on the geographical location. Genotype 1 subgroup a and genotype 3 are the most common in Scotland. HCV genotype 1 and particularly subgroup b, does not respond to therapy as well as genotypes 2 and 3.

Genotype details are as follows:

- Genotype 1a occurs in around 40% of patients
- Genotype 1b occurs in a small percentage of patients in Scotland, subtype 1b is difficult to eradicate using current medications; this type is most prevalent in Europe, Turkey, and Japan
- Genotypes 2 occurs in less than 5% of patients; these subtypes are most responsive to medication
- Genotypes 3 occur in around 50% of patients in Scotland; these subtypes are most prevalent in India, Pakistan, Thailand, Australia, and Scotland (IVDU population)
- Genotypes 4-6 occur in less than 5% of patients; it is most prevalent in the Middle East and Africa

Within a region, a specific genotype may also be associated with a specific mode of transmission, such as genotype 3 among persons in Scotland who abuse intravenous drugs.

Treatment of chronic HCV infection has 2 goals. The first is to achieve sustained eradication of HCV (i.e. sustained virologic response [SVR]), which is defined as the persistent absence of HCV RNA in serum 3 months or more after completing antiviral treatment. The second goal is to prevent progression to cirrhosis, hepatocellular carcinoma (HCC), and decompensate liver disease requiring liver transplantation.

Antiviral therapy for chronic hepatitis C should be determined on a case-by-case basis. However, treatment is generally recommended for patients with elevated serum ALT levels who meet the following criteria;

- Age greater than 18 years
- Positive HCV antibody and serum HCV RNA test results
- Willingness to be treated and to adhere to treatment requirements
- No contraindications for treatment

Current HCV Medications

The primary goal of HCV therapy is to cure the infection, which leads to a reduction of patients developing the complications of the virus including cirrhosis and hepatocellular cancer (HCC)

In patients who achieve a SVR, antiviral agents shorten the clinical course of HCV, prevent complications, prevent latent and/or subsequent recurrences, decrease transmission, and eliminate established latency.

The information in this pack gives a summary of the currently available treatments for hepatitis C. Please refer to the Summary of Product characteristics www.medicines.org.uk for full prescribing information and to University of Liverpool interaction checker at www.hep-druginteraction.org for drug interaction information.

The specialist clinical team is happy to be contacted for further information or queries.

Glecaprevir/Pibrentasvir (Maviret®)

Maviret is a combination tablet containing Glecaprevir 100mg and Pibrentasvir 40mg. Glecaprevir is a protease inhibitor and Pibrentasvir is a NS5A inhibitor.

Prescribing Information

Glecaprevir-pibrentasvir (Maviret) is a pangenotypic DAA which means it can be used to treat all Hepatitis C Genotypes (1-6). The treatment course length depends on the genotype, stage of liver disease and patients treatment history.

Dose is **3 Tablets (300/120mg)** taken by mouth **ONCE DAILY WITH or AFTER FOOD**

- For patients with no liver cirrhosis the course length is 8 weeks (All Genotypes)
- For patients with Compensated cirrhosis (Childs Pugh score A) the course length is 12 weeks
- For Genotype 3 patients with compensated cirrhosis who have had a previous treatment course for HCV and relapsed or failed treatment the course length is extended to 16 weeks.

Administration

The film coated tablet should be swallowed whole and not chewed or crushed. It should be administered after food to increase absorption.

Missed doses and Vomiting

If the patient vomits within 3 hours of taking a dose then they should be instructed to take another dose if however the vomiting occurs more than 3 hours after they have taken their dose then no further dose is required.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should not be instructed to take a double dose.

Pregnancy

As there is limited information on the use of Maviret in pregnancy it is not recommended for use in pregnancy.

Side Effects

Available trial data has shown Maviret to be relatively well tolerated with the most commonly reported side effects being headache and fatigue.

Drug Interactions

Please check the Summary of product information at www.medicines.org.uk for more detailed information about drug interactions and to check specific drugs use the interaction checker at www.hep-druginteractions.org.

Examples of drug interactions identified with Maviret are given below but this is not a complete list:

- Increased **Statin** levels requiring the statin dose to be adjusted
- **Ethinylestradiol** given in combination with Maviret has led to increased ALT levels and is not recommended.
- **Quetiapine** levels may be increased by co-administration of Maviret therefore this combination may sometimes not be appropriate if quetiapine toxicity could occur.
- **Antacids -** Medication which increases the gastric PH are expected to decrease the concentration of glecaprevir. Patients should be advised regarding timing of administration of Maviret and acid reducing medicines

Sofosbuvir/velpatasvir (Epclusa®)

Each Epclusa tablet contains Sofosbuvir 400mg with Velpatasvir 100mg.

Prescribing information

Epclusa is a pangenotypic drug meaning it can be used to treat all hepatitis C genotypes (1-6).

The usual treatment course is 12 weeks but can sometimes be reduced to 8 weeks in treatment naive Genotype 3 patients without cirrhosis.

Ribavirin may be added to Epclusa treatment in some Genotype 3 patients.

Administration

The usual dose is one tablet taken once daily with or without food. The tablet should not be crushed or chewed due to its bitter taste.

Missed doses

It is important to take this medication regularly to give the best chance of successful treatment.

If a dose is missed and the patient notices **less than 18 hours** after it should have been taken then the dose should be taken and then continue with the next dose at the prescribed time.

If a dose is missed and it is not noticed until **more than 18 hours** after it should have been taken then do not take that dose and continue with the usual dose at the prescribed time.

Vomiting

If a patient is sick **less than 3 hours** after taking an Epclusa tablet then another dose should be taken.

If a patient is sick **more than 3 hours** after taking an Epclusa tablet then another dose does not need to be taken.

Pregnancy and concomitant use with ribavirin

When sofosbuvir-velpatasvir (epclusa®) is used in combination with ribavirin, women of childbearing potential or their male partners must use two effective forms of contraception during the treatment and for a period of time after the treatment as recommended in the Summary of Product Characteristics for ribavirin.

Effects on ability to drive and use machines

sofosbuvir-velpatasvir (eplcusa®) has a negligible influence on the ability to drive and use machines. Patients should be informed that fatigue was more common in patients treated with sofosbuvir-velpatasvir (eplcusa®) than with placebo.

Side Effects

Epclusa has been found to be well tolerated and the most common side effects are fatigue and headache. A full list of adverse reactions can be found in the Summary of Product characteristics www.medicines.org.uk

Drug interactions

Use with potent P-gp and potent CYP inducers
Medicinal products that are potent P-glycoprotein (P-gp) or potent cytochrome P450 (CYP) inducers for example rifampicin, rifabutin, St. John's wort, carbamazepine and phenytoin will significantly decrease sofosbuvir or velpatasvir plasma concentrations and could result in loss of efficacy of Epclusa.

Use with Antacids
Adminstration of drugs which raise gastric PH can decrease the levels of Epclusa and decrease effectiveness. Therefore patients need to be carefully counseled about the appropriate choice of antacid and careful timing of antacid dosage while on Epclusa treatment. This includes OTC preparations.

Further information can be found at www.hep-druginteractions.org or from your specialist pharmacist.

Please check www.hep-druginteractions.org for all concomitant medications or consult with specialist pharmacist.

Special warnings and precautions for use

Epclusa should not be administered concurrently with other medicinal products containing sofosbuvir.

Severe bradycardia and heart block
Cases of severe bradycardia and heart block have been observed when sofosbuvir used in combination with another direct acting antiviral (DAA), is used with concomitant amiodarone.

Ledipasvir/Sofosbuvir (Harvoni®)

Ledipasvir/Sofosbuvir (Harvoni®) is a fixed dose combination tablet containing ledipasvir 90mg and sofosbuvir 400mg. Ledipasivir is a potent NS5A HCV inhibitor and sofosbuvir is a potent NS5B polymerase inhibitor. It is used in combination with sofosbuvir for treatment of genotype 1 and 4.

Prescribing Information

Harvoni is given as a single tablet containing 400mg of Sofosbuvir and 90mg of Ledipasvir swallowed whole once daily with or without food.

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) Genotype 1, 3 and 4 in adults. However is only listed in the current national guidelines for treatment of Genotype 1.

- Treatment-naïve Genotype 1 without cirrhosis: 8 weeks
- Treatment-experienced Genotype 1 without cirrhosis: 12 weeks
- Treatment naive or experienced Genotype1 with cirrhosis: 12 weeks +/- Ribavirin

Missed doses

Patients should be instructed that if vomiting occurs

- Within 5 hours of dosing an additional tablet should be taken.
- If vomiting occurs more than 5 hours after dosing, no further dose is needed

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed not to take a double dose.

Pregnancy and concomitant use with ribavirin

When ledipasvir/sofosbuvir (Harvoni®) is used in combination with ribavirin, women of childbearing potential or their male partners must use two effective forms of contraception during the treatment and for a period of time after the treatment as recommended in the Summary of Product Characteristics for ribavirin.

Side Effects

The most common adverse affects include headache, fatigue and less commonly rash.

Drug Interactions

For detailed information on drug interactions consults product information at www.medicines.org.uk or www.hep-druginteractions.org The information below gives some examples of potential interactions but is not a complete list.

Antacids

Coadministration of ledipasvir with acid-reducing agents may decrease ledipasvir solubility, resulting in decreased serum concentrations

Rosuvastatin

Levels of this statin may be increased by Harvoni leading to myopathy therefore this combination is not recommended.

Carbmazepine, Phenytoin, Rifampicin and St Johns Wort

These drugs can decrease the levels of Harvoni leading to treatment failure and should not be used in combination with Harvoni.

Mechanism of Interactions

Potential for Harvoni to affect other medicinal products

Ledipasvir is an *in vitro* inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of co-administered substrates for these transporters. *In vitro* data indicate that ledipasvir may be a weak inducer of metabolising enzymes such as CYP3A4, CYP2C and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with ledipasvir/sofosbuvir. *In vitro* ledipasvir inhibits intestinal CYP3A4 and UGT1A1. Medicinal products that have a narrow therapeutic range and which are metabolised by these isoenzymes should be used with caution and carefully monitored.

Potential for other medicinal products to affect Harvoni

Ledipasvir and sofosbuvir are substrates of drug transporter P-gp and BCRP while GS-331007 is not. Medicinal products that are potent P-gp inducers (e.g. rifampicin, St. John's wort, carbamazepine and phenytoin) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of ledipasvir/sofosbuvir and should not be used with Harvoni. Co-administration with medicinal products that inhibit P-gp and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS-331007 plasma concentration; Harvoni may be co-administered with P-gp and/or BCRP inhibitors. Clinically significant medicinal product interactions with ledipasvir/sofosbuvir mediated by CYP450s or UGT1A1 enzymes are not expected

Elbasvir/Grazoprevir (Zepatier®)

Prescribing Information

Each tablet contains Grazoprevir 100mg and Elbasvir 50mg.

For this drug regimen for some Genotypes if pre-treatment viral load is found to be >800,000 copies/ml then further polymorphism testing must be carried out to determine the optimum treatment regimen.

Genotype 1b Zepatier 1 daily for 12 weeks
Genotype 1a and 4 VL<800,000 copies/ml Zepatier 1 daily for 12 weeks
Genotype 1a and 4 VL>800,000 polymorphism test to determine if treatment should be extended to 16 weeks and ribavirin added.

Administration

Zepatier should be taken once daily with or without food. It should be swallowed whole not chewed or split. If Ribavirin is required this should be given twice daily with food.

Missed doses

It is important not to miss doses of this medication as taking it regularly will give the best chance of clearing the virus. If it is realised that a dose has been missed and it is **less than 16 hours** since it should have been taken then take it as soon as possible. If however it is **more than 16 hours late** then do not take that dose and continue with the next dose at the usual prescribed time.

Pregnancy and concomitant use with ribavirin

When Grazoprevir/Elbasvir (Zepatier®) is used in combination with ribavirin, women of childbearing potential or their male partners must use two effective forms of contraception during the treatment and for a period of time after the treatment as recommended in the Summary of Product Characteristics for ribavirin. Ribavirin is known to be teratogenic.

Effects on ability to drive and use machines

Grazoprevir/Elbasvir (Zepatier®) has a negligible influence on the ability to drive and use machines. Patients should be informed that fatigue was more common in patients treated with Grazoprevir/Elbasvir (Zepatier®) than with placebo.

Side effects

The most common side effects seen with Zepatier are fatigue and headache. A full list of side effects seen in clinical trials can be found on the SPC at www.medicines.org.uk

Drug interactions

Some drugs can affect Zepatier levels and should be avoided while a patient is on Zepatier treatment. These include drugs which induce P-Gp or CYP3A ad those which inhibit OATP1B or CYP3A.

Zepater can affect the levels of concomitant drugs including those eliminated via the BCRP or P-Gp pathways and these drugs may need to be adjusted while on Zepatier therapy. All drugs should be checked for interactions using www.hep-druginteractions.org or discuss with specialist pharmacist.

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®)

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) is a fixed dose combination tablet containing sofosbuvir 400mg and velpatasvir 100mg and.voxilaprevir 100mg. Sofosbuvir is an NS5B polymerase inhibitor, velpatasvir is a potent second generation NS5A HCV inhibitor and voxilaprevir is an NS3 protease inhibitor.

Prescribing Information

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) is indicated for treatment of chronic hepatitis C infection mono-infection and HCV/HIV-1 co-infection. It has been approved by the SMC for use in Scotland for patients who:

1: Have failed to achieve a sustained virologic response (SVR) with a direct-acting antiviral (DAA)

or

2: Are DAA-naïve, have genotype 3 (GT3) infection, with or without cirrhosis, and are suitable for treatment with an eight-week course.

In NHS Fife, sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) is currently only used for DAAexperienced patients (genotypes 1-6), with or without cirrhosis, at the following dose/duration.

• 1 tablet (400mg/100mg/100mg) taken by mouth once daily for 12 weeks

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) should not be used in patients with decompensated cirrhosis.

Administration

The film-coated tablet is for oral use. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed, due to the bitter taste of the active substance.

The tablet should be taken with food.

Missed doses

Patients should be instructed that if vomiting occurs within 4 hours of dosing, an additional tablet should be taken. If vomiting occurs more than 4 hours after dosing, no further dose is needed.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should not be instructed to take a double dose.

Pregnancy

There is limited data on use of sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) in pregnancy. As a precautionary measure, the manufacturer does not recommend use in pregnancy.

Effects on ability to drive and use machines

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) has a negligible influence on the ability to drive and use machines.

Summary of safety profile

Clinical trial data has shown that sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) is well tolerated. The most common side effects reported are headache, diarrhoea and nausea.

Drug-drug interactions Consult the SPC (www.medicines.org.uk) or www.hep-druginteractions.org for safety of concomitant meds or discuss with specialist clinical pharmacist.

Voxilaprevir is metabolised in vitro by CYP3A4 with the vast majority of drug in plasma being the parent drug. Velpatasvir and voxilaprevir are both inhibitors of drug transporters Pglycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3. Co-administration of sofosbuvir, velpatasvir and voxilaprevir with medicinal products that are substrates of these transporters may increase the exposure of the co-medications. This means that those where elevated plasma levels are associated with serious events are contraindicated and others may require dose adjustment or additional monitoring.

Rosuvastatin is contraindicated (due to BCRP and OATP1B inhibition by voxilaprevir and velpatasvir) as there is a 19-fold increase in plasma exposure of the statin. As this effect is likely to be attributed more to the BCRP transporter, other drugs that are a BCRP substrate including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, sulfasalazine and topotecan are also not recommended.

Caution is required with OATP1B inhibitors such as ciclosporin as voxilaprevir plasma exposure increases 19-fold, or with OATP1B substrates such as edoxaban as voxilaprevir inhibition is expected to increases the exposure of the factor Xa inhibitor. These combinations are both not recommended.

Concomitant use with medicinal products that are strong P-gp and/or strong cytochrome P450 (CYP) inducers such as rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital or phenytoin are contraindicated due to the decrease in sofosbuvir, velpatasvir and/or voxilaprevir exposure with the potential loss in

efficacy. However, there are also drugs that are moderate P-gp or CYP inducers (such as modafinil, efavirenz, oxcarbazepine and others) which can also reduce exposure of this DAA and currently these are also not recommended.

Community Supply of HCV Medication

Fife NHS Board has a commitment to deliver on the Scottish Government's policy initiative "Shifting the Balance of Care". The policy guidelines require improvements to health and social care services that improve the health and well-being of the population. In particular, changes are required so that the work of secondary care and primary care becomes more integrated and that care becomes located around community-based services.

The development of new medicines, like those for Hepatitis C (HCV), has meant that many treatments have become available that transform previously fatal or debilitating diseases into conditions that a patient may manage successfully for many years. Realising the investment in the patient's health requires that health services commit to normalising the patient's experience of care as much as possible, through integration with standard primary-care services.

For patients with HCV in Fife:

- The multidisciplinary hospital team will identify patients that fit the current guidelines for appropriate prescribing of HCV treatment.
- A start date will be agreed at a pre-treatment visit (usually in 3-4 weeks time).
- The hospital team will then make arrangements with the patient regarding which community pharmacy they would prefer to attend.
- They will then liaise with the community pharmacist to explain the procedure and arrange for the prescription to be posted to the pharmacy
- The community pharmacist dispenses the medication as per prescription and provides suitable information and advice to the patient.
- The community pharmacist should contact one of the Clinical Nurse Specialists or the Clinical Pharmacist if the patient fails to collect their medication or if there are any other concerns.

Contacts

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