NHS LOTHIAN

Community Pharmacy Supply of Medicines for Hepatitis C

Pharmaceutical Care Information Pack

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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. Until recently, HCV infection can be effectively treated with combination drug therapy (peginterferon alfa, ribavirin and the new directly-acting antivirals) with Sustained Viral Response (SVR) rates in 50-80% of patients.

Genotypes

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

Genotype details are as follows:

- Genotype 1 occurs in around 50% of patients in Lothian

- Genotypes 2 occurs in less than 5% of patients; these subtypes are most responsive to medication
- Genotypes 3 occur in around 45% of patients in Lothian; these subtypes are most prevalent in India, Pakistan, Thailand, Australia, and Scotland (PWID population)
- Genotype 4-6 occurs in less than 5% of patients; genotype 4 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
- Compensated liver disease (e.g. no hepatic encephalopathy or ascites)
- Acceptable hematologic and biochemical indices (hemoglobin at least 13 g/dL for men and 12 g/dL for women; neutrophil count >1500/mm^3, serum creatinine < 1.5 mg/dL)
- Willingness to be treated and to adhere to treatment requirements
- No contraindications for treatment

Guidance suggests that patients with normal liver enzyme levels and minimal liver fibrosis on ultrasound can elect to defer treatment until more effective and less toxic medications become available, whereas patients with more advanced liver injury prefer to initiate treatment sooner. Patients should be advised that the treatment of HCV infection in those with normal liver enzyme levels remains controversial.

The treatment of hepatitis C has evolved over the years. Initial studies used interferon (IFN) monotherapy. Traditionally, treatment consisted of combination therapy of ribavirin and IFN to which polyethylene glycol (PEG) molecules have been added to increase the half life, i.e. peginterferon (PEG-IFN). Protease inhibitors emerged as a third feature of combination therapy for patients with genotype 1 infection (G1). The first protease inhibitor indicated for use in HCV infection, boceprevir (Victrelis®), was approved by the EU approval July 2011 followed soon afterwards by telaprevir (Incivo®).

The creation of the new standard 'triple therapy' with the DAA (Directly Acting Antiretroviral) medications has led to significant improvements in the response rates for patients with G1 HCV, with SVR rates as high as 63–75% and reduction in duration of therapy by half for many patients based on response-guided therapy.

Whilst the appropriate use of protease inhibitors with peginterferon-ribavirin provided significant increases in cure rates of G1 chronic HCV infection, therapeutic options for HCV were still far from optimal. Many new side effects were encountered; drug interactions took on new importance and issues with resistance and intolerance persist, there is also an increased rate of adverse effects with the use of triple therapy.

Current HCV Medications

The primary goal of HCV therapy is to cure the infection and prevent transmission, 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 subsequent recurrences and decrease transmission.

Peginterferon alfa-2b (ViraferonPeg®)
PEG-IFN alfa-2b consists of IFN alfa-2b attached to a single 12-kd PEG chain. It is excreted by the kidneys. The adult dose is 1.5 mcg/kg subcutaneous (SC). The dose is sometimes reduced if required to ameliorate side effects- please refer to the SPC for details.

Peginterferon alfa-2a (Pegasys®)
PEG-IFN alfa-2a consists of IFN alfa-2a attached to a 40-kd branched PEG molecule. The adult dosage is 180 mcg via SC injection once weekly in the thigh or abdomen. The dose is sometimes reduced to 135 micrograms or 90 micrograms if required to ameliorate side effects.

In the treatment of hepatitis C, PEG-IFN is always used in combination with other antiviral medications.

Ribavirin (Rebetol®, Copegus®)
Ribavirin is an antiviral nucleoside analogue. Given alone, ribavirin has little effect on the course of hepatitis C. Given with IFN, it significantly augments the rate of sustained virologic response. Please refer to either the Copegus or Rebetol SPC as it gives further details on the dosing (based on weight and genotype)

Common side effects seen when using PEG-IFN plus ribavirin include flu-like symptoms, low mood, rash, dry skin, fatigue, anaemia, ophthalmic disturbance and GI disturbance. See summary of product characteristics for further information (www.medicines.org.uk)

Boceprevir (Victrelis®)
NS3/4A protease inhibitors interfere with the ability of HCV to replicate by inhibiting a key viral enzyme, NS3/4A serine protease. Boceprevir inhibits replication of the hepatitis C virus by binding reversibly to NS3 serine protease. Boceprevir must be administered in combination with PEG-INF alfa and ribavirin. The dosage is 800 mg orally 3 times daily. Boceprevir is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

Telaprevir (Incivo®)
Telaprevir inhibits HCV NS3/4A protease needed for proteolytic cleavage of the HCV-encoded poly-protein into mature forms. It is indicated for chronic hepatitis C genotype 1 infection in combination with peginterferon alfa and ribavirin. Indication is specifically for adults with compensated liver disease, including cirrhosis, who are treatment-naive or who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.

Newly licensed agents

Directly Acting Antiretrovirals (DAAs)

Sofosbuvir - NS5B Polymerase Inhibitor

Sofosbuvir (SOF) is an HCV-specific uridine nucleotide prodrug that blocks replication of HCV by inhibiting the HCV NS5B polymerase and terminating the generation of HCV RNA chains.

Unlike the majority of available drugs, SOF and its major metabolite, GS-331007, are not metabolised by the cytochrome (CYP) P450 enzymes or by uridine biphosphate glucuronosyltransferase (UGT) and do not act as inducers or inhibitors of these enzymes.

SOF, but not GS-331007, is a substrate of both drug transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP), therefore medicinal products which are potent inducers of these pathways have the potential to affect SOF metabolism and reduce its concentration and therapeutic efficacy. Although interactions have not been directly studied, co-administration with the analeptic modafinil, with certain anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital, oxcarbazepine), with some antimycobacterials (e.g. rifabutin, rifampicin, rifapentine) or with St John's Wort, all potent inducers of P-gp, is expected to decrease the concentration of SOF leading to reduced therapeutic effect. Sofosbuvir should not be used with such products.

The US prescribing data has recently been updated to advise that concurrent use of amiodarone with sofosbuvir, is not recommended due to symptomatic bradycardia.

Consult the summary of product characteristics (www.medicines.org.uk), University of Liverpool interaction website (www.hep-druginteractions.org) for safety of concomitant meds or discuss with specialist clinical pharmacist.

Prescribing Information

Sofosbuvir is indicated for treatment of chronic hepatitis C infection as a component of a combination antiviral regimen for patients with HCV mono-infection and HCV/HIV-1 co-infection. The treatment regimen and duration are dependent on both viral genotype and patient population

- Genotype 1 or 4:

  400 mg PO daily plus ribavirin and peginterferon alfa for 12 weeks; may consider Sofosbuvir plus ribavirin for 24 weeks in genotype 1 patients ineligible to receive peg-interferon-based regimen

- Genotype 2

  400 mg PO daily plus ribavirin for 12 weeks (SMC restriction for use only in treatment-naive patients who are ineligible for, or are unable to tolerate, peginterferon alfa)

- Genotype 3

400 mg PO daily plus peginterferon alfa and ribavirin for 12 weeks, may consider Sofosbuvir plus ribavirin for 24 weeks in patients ineligible to receive peg-interferon-based regimen

Dosing Considerations
Sofosbuvir must not be used as monotherapy; if peginterferon alfa or ribavirin is discontinued for any reason, sofosbuvir must also be discontinued

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 if possible although efficacy on an empty stomach is not affected to any clinically significant extent (as per Sovaldi SPC, Gilead 2014)

Missed doses
Patients should be instructed that if vomiting occurs within 2 hours of dosing an additional tablet should be taken. If vomiting occurs more than 2 hours after dosing, no further dose is needed. These recommendations are based on the absorption kinetics of sofosbuvir and GS-331007 suggesting that the majority of the dose is absorbed within 2 hours after dosing.

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 and concomitant use with ribavirin
When sofosbuvir is used in combination with ribavirin or peginterferon alfa/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 has moderate influence on the ability to drive and use machines. Patients should be informed that fatigue and disturbance in attention, dizziness and blurred vision have been reported during treatment with sofosbuvir in combination with peginterferon alfa and ribavirin.

Summary of safety profile
Sofosbuvir has mainly been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse drug reactions occurring in subjects receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

Ledipasvir - NS5A inhibitor + Sofosbuvir - NS5B Polymerase Inhibitor (Harvoni®)

Ledipasvir-Sofosbuvir (Harvoni®) is a fixed dose combination tablet containing ledipasvir 90mg and sofosbuvir 400mg. Ledipasivir is a potent NS5A HCV inhibitor. The NS5A protein is essential for viral assembly and replication. It is used in combination with sofosbuvir for treatment of genotype 1, 3 and 4.

The interaction profile for ledipasvir-sofosbuvir (harvoni®) is similar to that of sofosbuvir as detailed above and any interactions identified for sofosbuvir may occur with ledipasvir-sofosbuvir (harvoni®).

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP and may increase intestinal absorption of coadministered substrates for these transporters. P-gp inducers (e.g., rifampicin or St. John's Wort) may decrease ledipasvir and sofosbuvir plasma concentrations, leading to reduced therapeutic effect of ledipasvir-sofosbuvir (harvoni®), and the use with P-gp inducers is not recommended with ledipasvir-sofosbuvir (harvoni®)

Clinically significant medicinal product interactions with ledipasvir-sofosbuvir (harvoni®) mediated by CYP450s or UGT1A1 enzymes are not expected.

Further interactions specific to ledipasvir, are co-administration with acid reducing agents. Ledipasvir solubility decreases as pH increases. Medicinal products that increase gastric pH are expected to decrease concentration of ledipasvir. Therefore patients should be advised regarding timing and maximum doses of administration of ledipasvir-sofosbuvir (harvoni®) and acid reducing medicines. Details can be found in the SPC but this may have relevance for patients purchasing OTC acid reducing medicines.

Due to effect on drug transporters, ledipasvir may also affect HMG- CoA Reductase Inhibitors (Statins). Details of individual interactions can be found in the SPC.

Consult the summary of product characteristics (www.medicines.org.uk) or www.hep-druginteractions.org for safety of concomitant meds or discuss with specialist clinical pharmacist.

Prescribing Information

Ledipasvir-sofosbuvir (harvoni®)® is indicated for treatment of chronic hepatitis C infection mono-infection and HCV/HIV-1 co-infection. The treatment regimen and duration are dependent on both viral genotype and patient population. The current license recommends treatment courses up to 24 weeks. However, subsequent trial information has shown comparable results with course length shortened to 12 weeks, even if patient has been shown to be cirrhotic and/or treatment experienced. Therefore, in the vast majority of cases, treatment will be given for 12 weeks.

- Genotype 1 or 4 advanced fibrosis or cirrhosis

1 tablet (90mg/400mg) PO daily plus ribavirin 12 weeks;

  - In patients who are treatment naïve and non-cirrhotic, treatment can be shortened to 8 weeks of ledipasvir-sofosbuvir (harvoni®) only (ie no ribavirin)

- Genotype 3

1 tablet (90mg/400mg) PO daily plus ribavirin for 12 weeks. Note this treatment regimen is NOT RECOMMENDED by SMC and therefore requires IPTR approval before it can be prescribed for an individual patient.

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 or without food.

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 not be instructed 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.

Effects on ability to drive and use machines
Ledipasvir-sofosbuvir (harvoni®) 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 ledipasvir-sofosbuvir (harvoni®) than with placebo.

Summary of safety profile
The adverse effect profile of sofosbuvir is detailed above. Clinical trial data has shown that ledipasvir-sofosbuvir (harvoni®) is well tolerated with the most common side effects reported are fatigue and headache.

Simeprevir - Protease Inhibitor

Similar to telaprevir and boceprevir, simeprevir is a NS3/4A protease inhibitor. Its mechanism of action is similar to other protease inhibitors which are currently approved to treat genotype 1 HCV infection. Patients with genotype 1a will be tested for presence of Q80k polymorphism. Studies have shown that patients without this polymorphism have a higher likelihood of SVR (cure).

Simeprevir (SIM) is highly effective in treating treatment-naive and treatment-experienced patients. In addition to being highly efficacious, simeprevir also appears to be safe with relatively few adverse side effects.

The incidence of anaemia and rash appears to be lower compared to telaprevir and boceprevir. Unlike telaprevir and boceprevir, which need to be administered every multiple times a day with a fatty meal or snack; simeprevir can be taken as once-daily dosing with food. This should theoretically improve patient compliance with HCV therapy.

Prescribing Information

Duration of Treatment
In all patients, treatment with simeprevir should be initiated in combination with other medicinal products and should be administered for 12 weeks.

- All treatment-naïve and prior relapse patients, including those with cirrhosis, should receive an additional 12 weeks of peginterferon alfa and ribavirin after completing 12 weeks of treatment with simeprevir, peginterferon alfa and ribavirin (total treatment duration of 24 weeks).

- Patients with proven intolerance to interferon with advanced disease requiring treatment, simeprevir will be used in combination with sofosbuvir for 12 weeks. Consideration should be given to addition of ribavirin depending on clinical circumstances

The dose is 150mg once daily, swallowed whole with food.

Missed doses
If a dose of simeprevir is missed, and the patient notices within 12 hours of the usual dosing time, the patient should take the missed dose of simeprevir with food as soon as possible and then take the next dose of simeprevir at the regularly scheduled time.

If a dose of simeprevir is missed by more than 12 hours after the usual dosing time, the patient should not take the missed dose of simeprevir and should resume dosing of simeprevir with food at the regularly scheduled time.

Dosage Adjustment or Interruption
To prevent treatment failure, the dose of simeprevir must not be reduced or interrupted. If treatment with simeprevir is discontinued because of adverse reactions or inadequate on-treatment virologic response, treatment must not be reinitiated. If adverse reactions potentially related to peginterferon alfa and/or ribavirin occur which require dosage adjustment or interruption of either medicine, refer to the instructions outlined in the respective prescribing information for these medicines.

Photosensitivity
Photosensitivity reactions have been observed with simeprevir in combination with peginterferon alfa and ribavirin, including serious reactions which resulted in hospitalisation. Photosensitivity reactions occurred most frequently in the first 4 weeks of treatment with simeprevir in combination with peginterferon alfa and ribavirin, but can occur at any time during treatment. Photosensitivity may present as an exaggerated sunburn reaction, usually affecting areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, and dorsa of the hands). Manifestations may include burning, erythema, exudation, blistering, and oedema.

Use sun protective measures and limit sun exposure during treatment with simeprevir in combination with peginterferon alfa and ribavirin. Avoid use of tanning devices during treatment with simeprevir in combination with peginterferon alfa and ribavirin. Discontinuation of simeprevir should be considered if a photosensitivity reaction occurs but this decision should only by made by a senior member of the specialist hepatitis prescribing team (contact on call medic out of hours if necessary) and patients should be monitored until the reaction has resolved.

Rash
Rash has been observed in subjects receiving simeprevir in combination with peginterferon alfa and ribavirin. Rash occurred most frequently in the first 4 weeks of treatment with simeprevir in combination with peginterferon alfa and ribavirin, but can occur at any time during treatment. Severe rash and rash requiring discontinuation of simeprevir have been reported. Most of the rash events in simeprevir-treated patients were of mild or moderate severity. Patients with mild to moderate rashes should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, simeprevir should be discontinued, again only after contact is made with member of the specialist prescribing team. Patients should be monitored until the rash has resolved.

Discontinue if inadequate virologic response

- Monitor HCV RNA levels to determine virologic response
- It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR), therefore discontinuation of treatment is recommended in these patients
- HCV-RNA levels at week 4 ≥25 IU/mL: Discontinue simeprevir, peginterferon alfa, and ribavirin
- HCV-RNA levels at week 12 detectable: Discontinue peginterferon alfa and ribavirin (treatment with simeprevir completed at week 12)

Dosage Modifications / Considerations

- To prevent treatment failure, the dose must not be reduced or interrupted
- If treatment is discontinued because of adverse reactions or inadequate on-treatment virologic response, simeprevir must not be reinitiated
- If adverse reactions potentially related to peginterferon alfa and/or ribavirin occur which require dosage adjustment or interruption of either medicine, refer to the instructions outlined in the respective prescribing information for these medicines
- Must not be used as monotherapy; if peginterferon alfa or ribavirin is discontinued for any reason, simeprevir must also be discontinued

- Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism

Metabolism

Substrate: CYP3A (major); CYP2C8 (minor) and CYP2C19 (minor)

Inhibits OATP1B1/3 and P-gp transporters

Mildly inhibits CYP1A2 and intestinal CYP3A, but does not affect hepatic CYP3A4 activity

Simeprevir is primarily metabolized via CYP3A enzymes and thus administering simeprevir with medications that have moderate or strong induction of CYP3A may significantly reduce levels of simeprevir (examples include rifampicin, St. John's Wort, and anticonvulsants carbamazepine, oxcarbazepine, phenytoin and phenobarbital). In contrast, medications that have moderate or strong inhibition of CYP3A may significantly increase levels of simeprevir, including clarithromycin, ketoconazole, ritonavir, and Silybum marianum (milk thistle). Accordingly, simeprevir should not be given with moderate or strong inducers or inhibitor of CYP3A. Simeprevir is an inhibitor of CYP1A2 and intestinal CYP3A, but not hepatic CYP3A4. Levels of medications that undergo primary metabolism via CYP3A4 may increase if coadministered with simeprevir.

Co-administration of simeprevir with medicinal products that are substrates for OATP1B1 and P-gp transport may result in increased plasma concentrations of such medicinal products

Consult summary of product characteristics (www.medicines.org.uk), www.hep-druginteractions.org for safety of concomitant meds or discuss with specialist clinical pharmacist.

Daclatasvir NS5A polymerase inhibitor

Daclatasvir (DCV) is a NS5A complex inhibitor. The NS5A protein is essential for viral assembly and replication. Daclatasvir is used in combination with other antiviral medicines and has been shown to be effective in genotypes 1, 3 and 4.

Prescribing Information

Duration of Treatment
In NHS Lothian, daclatasvir can be used in patients in line with SMC restriction ie patients with significant fibrosis or compensated cirrhosis, who are ineligible for interferon (such as intolerance or risk of decompensation of liver disease) In all patients, treatment with daclatasvir should be initiated in combination with sofosbuvir as follows

Genotype 1 and 4

- In patients with significant fibrosis, daclatasvir plus sofosbuvir for 12 weeks

- In patients with compensated cirrhosis, daclatasvir plus sofosbuvir for 24 weeks

Genotype 3

- Daclatasvir plus sofosbuvir plus ribavirin for 24 weeks. Consideration may be given to reducing the course length to 12 weeks in patients with less severe fibrosis. This takes into account emerging data showing good outcomes with the reduced course length of 12 weeks.

Administration

The dose of daclatasvir is 60mg once daily, taken with or without meals. The film coated tablet should swallowed whole and not chewed or crushed due to the unpleasant taste of the active substance.

Missed doses

Patients should be instructed that, if they miss a dose of daclatasvir, the dose should be taken as soon as possible if remembered within 20 hours of the scheduled dose time. However, if the missed dose is remembered more than 20 hours after the scheduled dose, the dose should be skipped and the next dose taken at the appropriate time.

Metabolism

Daclatasvir is a substrate of CYP3A4 and P-gp. Strong or moderate inducers of CYP3A4 or P-gp may decrease the plasma levels and therapeutic effect of daclatasvir. Co-administration with strong inducers of CYP3A4 and P-gp is contraindicated. eg phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, systemic dexamethasone and the herbal product St John's Wort (*hypericum perforatum*). Co-administration may lead to lower exposure and loss of efficacy. Co-administration with moderate inducers requires dose adjustment of daclatasvir to 90mg once daily

Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir. Dose adjustment of daclatasvir to 30mg once daily is recommended when co administered with strong inhibitors of CYP3A4. Co administration of medicines that inhibit P-gp activity is likely to a have limited effect on daclatasvir exposure.

Daclatasvir is also an inhibitor of, organic anion transporting polypeptide (OATP) 1B1, organic-cation transporter (OCT)1 and breast cancer resistance protein (BCRP). Administration of daclatasvir may increase systemic exposure to medicinal products that are substrates of P-gp, OATP 1B1, OCT1 or BCRP, which could increase or prolong their therapeutic effect and adverse reactions. Caution should be used if the medicinal product has a narrow therapeutic range.

Consult the summary of product characteristics (www.medicines.org.uk) , www.hep-druginteractions.org for safety of concomitant meds or discuss with specialist clinical pharmacist.

Pregnancy and concomitant use with ribavirin

When daclatasvir 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
Dizziness has been reported during treatment with daclatasvir in combination with sofosbuvir, and dizziness, disturbance in attention, blurred vision and reduced visual acuity have been reported during treatment with daclatasvir in combination with peginterferon alfa and ribavirin

Summary of the safety profile
The most frequently reported adverse reactions were fatigue, headache, and nausea. No Grade 3 or 4 adverse reactions were reported in the clinical studies for daclatasvir.

Community Supply of HCV Medication

NHS Lothian 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 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.

To achieve these aims for patients with HCV in Lothian the multidisciplinary hospital team led by the prescribing consultants will identify patients that fit the current guidelines for appropriate prescribing of the HCV agent. A start date (usually in 4 weeks time) will be agreed at pre- treatment visit and the specialist clinical pharmacist will then make arrangements with the patient (via Clinical Nurse Specialists) for which community pharmacy they will attend. They will ensure prescription is legal and liaise with community pharmacist to allow seamless supply chain and cover of any issues that may arise. The specialist pharmacy team will provide all the suitable patient specific information and guidance to enable the community pharmacist to provide pharmaceutical care to the patient. The specialist pharmacy team will inform the community pharmacy when a prescription for the patient has been issued. The prescription will contain the patient's community health index (CHI) number and an indication of whether there is a need for instalment dispensing its frequency and if supervision is required after a discussion with the community pharmacist.

The community pharmacist will order sufficient medication from the pharmaceutical company or their wholesaler to ensure continuous treatment of the patient. The community pharmacist will discuss the service they provide with the patient at presentation and consider if registration for the Chronic Medication Service is appropriate. The community pharmacist will provide suitable information and advice to the patient to enable them to take their medicines accurately and appropriately and to manage any adverse effects that they may experience. The community pharmacist will contact the specialist clinical pharmacist (or clinical nurse specialist when clinical pharmacist absent) during working hours if the patient is experiencing problems, stops treatment or fails to collect their treatment when they require a further supply.

The scope of items which may be dispensed by community pharmacy contractors through this specification will be subject to local board formulary advice. Inclusion in local board formulary will reflect existing good clinical practice and SMC advice.

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