Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
http://www.gmc-uk.org/mobile/14327

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Glecaprevir/pibrentasvir 100 mg / 40 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg glecaprevir and 40 mg pibrentasvir.

Excipient with known effect
Each film-coated tablet contains 7.48 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, oblong, biconvex, film-coated tablet of dimensions 18.8 mm x 10.0 mm, debossed on one side with '2nd'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the context of the Early Access to Medicines Scheme, glecaprevir/pibrentasvir is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated cirrhosis and at least one of the following:

- GT 1, 4, 5 or 6-infected patients previously treated with NS5A inhibitors
- GT 2, 3, 5 or 6-infected patients with chronic kidney disease (stage 4 and 5)
- GT 3-infected patients previously treated with peg-interferon, ribavirin, and/or sofosbuvir.

4.2 Posology and method of administration

Glecaprevir/pibrentasvir treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Posology
The recommended dose of glecaprevir/pibrentasvir is three tablets, taken orally, once daily with food (see section 5.2).

The recommended glecaprevir/pibrentasvir treatment duration for patients eligible to participate in the EAMS are described below:

Table 1: Recommended durations of treatment for compensated cirrhotic patients without chronic kidney disease

Patient Population	Recommended Treatment Duration
GT 1, 4, 5, 6 NS5A inhibitor-experienced	16 weeks
GT 3 Previously treated with peg-interferon, ribavirin, and/or sofosbuvir - no prior exposure to a NS5A inhibitor	

Table 2: Recommended durations of treatment for compensated cirrhotic patients with chronic kidney disease

Patient Population	Recommended Treatment Duration
GT 1, 4, 5 or 6 NS5A inhibitor-experienced	16 weeks
GT 2, 5 or 6 No prior exposure to a NS5A inhibitor	12 weeks
GT 3 Previously treated with peg-interferon, ribavirin, and/or sofosbuvir - no prior exposure to a NS5A inhibitor	16 weeks

Missed dose
In case a dose of glecaprevir/pibrentasvir is missed, the prescribed dose can be taken within 18 hours. If more than 18 hours have passed since glecaprevir/pibrentasvir is usually taken, the missed dose should **not** be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

Renal impairment
No dose adjustment of glecaprevir/pibrentasvir is required in patients with any degree of renal impairment including patients on dialysis (see section 5.2).

Hepatic impairment
No dose adjustment of glecaprevir/pibrentasvir is required in patients with mild hepatic impairment (Child-Pugh A).Patients with severe hepatic impairment (Child-Pugh C) or moderate hepatic impairment (Child-Pugh B) are not eligible to be treated within EAMS.

Elderly
No dose adjustment of glecaprevir/pibrentasvir is required in elderly patients (see sections 5.1 and 5.2).

Method of administration
For oral use.

Patients should be instructed to swallow tablets whole with food and not to chew, crush or break the tablets (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Patients with severe hepatic impairment (Child-Pugh C) or moderate hepatic impairment (Child-Pugh B) are not eligible to be treated within EAMS.

Concomitant use with atazanavir and rifampicin (see section 4.5).

Patients who are pregnant or breastfeeding are not eligible to be treated within EAMS.

4.4 Special warnings and precautions for use

Hepatitis B Virus reactivation
Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Lactose
Glecaprevir/pibrentasvir contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for glecaprevir/pibrentasvir to affect other medicinal products
Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Glecaprevir/pibrentasvir may increase concentrations of medicinal products that are substrates for P-gp (i.e. digoxin, dabigatran etexilate), BCRP (i.e. rosuvastatin, sofosbuvir), and OATP1B1/3 (i.e. pravastatin, rosuvastatin, atorvastatin, simvastatin, lovastatin, valsartan). Specific recommendations are provided below for drugs evaluated in combination with glecaprevir/pibrentasvir. For other medicinal products, refer to respective literature for guidance on use with inhibitors of P-gp, BCRP, and OATP1B1/3. Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2 and uridine glucuronosyltransferase (UGT) 1A1. Significant interactions are not expected when glecaprevir/pibrentasvir is co-administered with substrates of CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2D6, UGT1A1, or UGT1A4.

Patients treated with vitamin K antagonists
As liver function may change during treatment with glecaprevir/pibrentasvir, a close monitoring of International Normalised Ratio (INR) values is recommended.

Potential for other medicinal products to affect glecaprevir/pibrentasvir
Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Drugs that are strong inhibitors of OATP1B1/3 (i.e. darunavir, lopinavir) may significantly increase concentrations of glecaprevir and are not recommended.

Co-administration of glecaprevir/pibrentasvir with medicinal products that inhibit P-gp and/or BCRP (i.e. cobicistat, ritonavir) are not expected to cause any clinically significant changes in glecaprevir or pibrentasvir concentrations.

Co-administration of glecaprevir/pibrentasvir with medicinal products that induce P-gp/CYP3A (i.e. carbamazepine, efavirenz, St. John's wort [hypericum perforatum]) may decrease glecaprevir and pibrentasvir plasma concentrations, therefore, co-administration is not recommended. No selective inducers of BCRP have been identified.

Established and other potential medicinal product interactions

Table 3 details on the effect on concentration of glecaprevir/pibrentasvir and concomitant medicinal products. The direction of the arrow indicates the direction of the change in exposures (Cmax and AUC) in glecaprevir, pibrentasvir, and the co-administered medicinal product (↑ = increase (more than 25%), ↓ = decrease (more than 20%), ↔ = no change (equal to or less than 20% decrease or 25% increase).

Table 3: Interactions between Glecaprevir/pibrentasvir and other medicinal products

Medicinal product by therapeutic areas/possible mechanism of interaction	Effect on medicinal product levels	Clinical Comments
ANTIARRHYTHMICS		
Digoxin 0.5 mg single dose (Inhibition of P-gp)	↑ digoxin	Digoxin dose should be reduced by 50% when co-administered with glecaprevir/pibrentasvir.
ANTICOAGULANTS		
Dabigatran etexilate 150 mg single dose (Inhibition of P-gp)	↑ dabigatran	Co-administration is not recommended.
ANTICONVULSANTS		
Carbamazepine 200 mg twice daily (Induction of P-gp/CYP3A)	↓ glecaprevir ↓ pibrentasvir	Co-administration may lead to reduced therapeutic effect of glecaprevir/pibrentasvir and is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin 600 mg single dose (Inhibition of OATP1B1/3)	↑ glecaprevir ↔ pibrentasvir	Co-administration is contraindicated (see section 4.3).
Rifampicin 600 mg once daily[a] (Induction of P-gp/CYP3A)	↓ glecaprevir ↓ pibrentasvir	
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*) (Induction of P-gp/CYP3A)	Not studied. Expected: ↓ glecaprevir and ↓ pibrentasvir	Co-administration may lead to reduced therapeutic effect of glecaprevir/pibrentasvir and is not recommended.
HIV-ANTIVIRAL AGENTS		
Atazanavir + ritonavir 300/100 mg once daily[b]	↑ glecaprevir ↑ pibrentasvir	Co-administration is contraindicated (see section 4.3).
Darunavir + ritonavir 800/100 mg once daily	↑ glecaprevir ↔ pibrentasvir	Co-administration is not recommended.

Efavirenz/emtricitabine/tenofovir disoproxil fumarate	The effect of efavirenz/emtricitabine/TDF on glecaprevir and pibrentasvir was not evaluated within this study, but glecaprevir and pibrentasvir exposures were significantly lower than in other studies of similar doses.	Co-administration with efavirenz may lead to reduced therapeutic effect of glecaprevir/pibrentasvir and is not recommended.
Lopinavir/ritonavir 400/100 mg once daily	↑ glecaprevir ↑ pibrentasvir	Co-administration is not recommended.
HMG-COA REDUCTASE INHIBITORS		
Pravastatin 10 mg once daily (Inhibition of OATP1B1/3)	↑ pravastatin	Pravastatin dose should be reduced by 50% and rosuvastatin dose should not exceed 10 mg per day when co-administered with Glecaprevir/pibrentasvir.
Rosuvastatin 5 mg once daily (Inhibition of OATP1B1/3, BCRP)	↑ rosuvastatin	
Atorvastatin 10 mg once daily (Inhibition of OATP1B1/3, CYP3A)	↑ atorvastatin	Co-administration is not recommended. Consider alternative therapies, such as pravastatin or rosuvastatin.
Lovastatin 10 mg once daily	↑ lovastatin ↑ lovastatin acid	
Simvastatin 5 mg once daily	↑ simvastatin ↑ simvastatin acid	
IMMUNOSUPPRESSANTS		
Ciclosporin 100 mg single dose	↑ glecaprevir ↑ pibrentasvir	Glecaprevir/pibrentasvir is not recommended for use in patients requiring stable ciclosporin doses > 100 mg per day. Glecaprevir/pibrentasvir may be initiated in subjects receiving ciclosporin ≤ 100 mg per day and ciclosporin doses may be adjusted up to 400 mg per day following standard therapeutic monitoring practices.
Ciclosporin 400 mg single dose	↑ glecaprevir ↑ pibrentasvir	
ETHINYLOESTRADIOL-CONTAINING PRODUCTS		
Ethinyloestradiol (EE)/Norgestimate 35 µg/250 µg once daily	↑ EE ↑ norgestromin ↑ norgestrel	Co-administration of glecaprevir/pibrentasvir with ethinyloestradiol-containing products may increase the risk of ALT elevations and is not recommended.
EE/Levonorgestrel 20 µg/100 µg once daily	↑ EE ↑ norgestrel	
VITAMIN K ANTAGONISTS		
Vitamin K antagonists	Not studied.	Close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver

		function changes during treatment with glecaprevir/pibrentasvir.

Medicinal products without clinically significant interactions with glecaprevir/pibrentasvir
No dose adjustment is required when glecaprevir/pibrentasvir is co-administered with the following medications: abacavir, amlodipine, buprenorphine, caffeine, dextromethorphan, dolutegravir, elvitegravir/cobicistat, emtricitabine, felodipine, lamivudine, lamotrigine, losartan, methadone, midazolam, naloxone, norethindrone or other progestin-only contraceptives, omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir alafenamide, tenofovir disoproxil fumarate, tolbutamide and valsartan.

4.7 Effects on ability to drive and use machines

Glecaprevir/pibrentasvir has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The safety assessment for glecaprevir/pibrentasvir in subjects with compensated liver disease (with or without cirrhosis) were derived from Phase 2 and 3 studies which evaluated approximately 2,300 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received glecaprevir/pibrentasvir for 8, 12 or 16 weeks.

The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received glecaprevir/pibrentasvir.

Across the Phase 2 and 3 clinical studies, adverse reactions with a frequency of very common (incidence ≥ 10%) were headache and fatigue in subjects treated with glecaprevir/pibrentasvir for 8, 12 or 16 weeks. Nausea was observed with a frequency of common (incidence ≥ 5% and < 10%).

The type and severity of adverse reactions in subjects with cirrhosis were comparable to those seen in subjects without cirrhosis.

In subjects with chronic kidney disease (Stage 4 or Stage 5 including subjects on dialysis) and genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection with compensated liver disease (with or without cirrhosis), adverse reactions with a frequency of very common (incidence ≥ 10%) were pruritus and fatigue in subjects treated with for 12 weeks. Nausea, asthenia, and headache were observed with a frequency of common (incidence ≥ 5% and < 10%) in subjects receiving 12 weeks of treatment with. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 1.9%.

Paediatric population
No data are available.

4.9 Overdose

The highest documented doses administered to healthy volunteers is 1200 mg once daily for 7 days for glecaprevir and 600 mg once daily for 10 days for pibrentasvir. In case of overdose, the patient should be monitored for any signs and symptoms of toxicities. Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir are not significantly removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: not yet assigned

Mechanism of action
Glecaprevir/pibrentasvir is a fixed-dose combination of two pan-genotypic, direct-acting antiviral agents, glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor), targeting multiple steps in the HCV viral lifecycle.

5.2 Pharmacokinetic properties

Pharmacokinetics in special populations
Race/ethnicity
No dose adjustment of glecaprevir/pibrentasvir is required based on race or ethnicity.

Gender/weight
No dose adjustment of glecaprevir/pibrentasvir is required based on gender or body weight.

Elderly
No dose adjustment of glecaprevir/pibrentasvir is required in elderly patients. Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 88 years) analysed, age did not have a clinically relevant effect on the exposure to glecaprevir or pibrentasvir.

Renal Impairment
Glecaprevir and pibrentasvir AUC were increased ≤ 56% in non-HCV infected subjects with mild, moderate, severe, or end-stage renal impairment not on dialysis compared to subjects with normal renal function. Glecaprevir and pibrentasvir AUC were similar with and without dialysis (≤ 18% difference) in dialysis-dependent non-HCV infected subjects. In population pharmacokinetic analysis of HCV-infected subjects, 86% higher glecaprevir and 54% higher pibrentasvir AUC were observed for subjects with end stage renal disease, with or without dialysis, compared to subjects with normal renal function.

Overall, the changes in exposures of glecaprevir/pibrentasvir in HCV-infected subjects with renal impairment with or without dialysis were not clinically significant.

Hepatic Impairment
At the clinical dose, compared to non-HCV infected subjects with normal hepatic function, glecaprevir AUC was 33% higher in Child-Pugh A subjects, 100% higher in Child-Pugh B subjects, and increased to 11-fold in Child-Pugh C subjects. Pibrentasvir AUC was similar in Child-Pugh A subjects, 26% higher in Child-Pugh B subjects, and 114% higher in Child-Pugh C subjects.

Population pharmacokinetic analysis demonstrated that following administration of glecaprevir/pibrentasvir in HCV infected subjects with compensated cirrhosis, exposure of glecaprevir was approximately 2-fold and pibrentasvir exposure was similar to non-cirrhotic HCV infected subjects.

Paediatric Patients
The pharmacokinetics of glecaprevir/pibrentasvir in paediatric patients have not been established (see section 4.2).

5.3 Preclinical safety data

Glecaprevir and pibrentasvir were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial

mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rodent micronucleus assays. Carcinogenicity studies with glecaprevir and pibrentasvir have not been conducted.

No effects on mating, female or male fertility, or early embryonic development were observed in rodents at up to the highest dose tested. Systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 63 and 102 times higher, respectively, than the exposure in humans at the recommended dose.

In animal reproduction studies, no adverse developmental effects were observed when the components of glecaprevir/pibrentasvir were administered separately during organogenesis at exposures up to 53 and 0.07 times (rats and rabbits, respectively; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) higher than the human exposures at the recommended dose of glecaprevir/pibrentasvir. In rabbits, maternal toxicity (anorexia, lower body weight, and lower body weight gain), associated with embryo-foetal loss precluded the ability to evaluate glecaprevir at clinical exposure levels. A risk of embryo-foetal toxicity cannot be excluded. There were no effects with either compound in rodent peri/postnatal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 47 and 74 times higher, respectively, than the exposure in humans at the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Copovidone (Type K 28)
Vitamin E (tocopherol) Polyethylene Glycol Succinate
Silica, colloidal anhydrous
Propylene Glycol Monocaprylate (Type II)
Croscarmellose Sodium
Sodium Stearyl Fumarate

Film Coating:
Hypromellose 2910 (E464)
Lactose Monohydrate
Titanium Dioxide
Macrogol 3350
Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store this medicine below 30° C in the original package to protect from moisture.

Keep the bottle tightly closed.

6.5 Nature and contents of container

Glecaprevir/pibrentasvir tablets are supplied in high density polyethylene bottles with child resistant polypropylene caps containing 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. EAMS NUMBER

41042/0002

9. DATE OF SCIENTIFIC OPINION

09/05/2017

Additional information:
[The Applicant should insert here any additional relevant information if required e.g. check lists, dose adjustment charts]

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