21 November 2013
EMA/24463/2014
Evaluation of Medicines for Human Use

Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring adressed to member states for Daclatasvir available for compassionate use

1. MEDICINAL PRODUCT FOR COMPASSIONATE USE

- **Name of the medicinal product for Compassionate Use: daclatasvir**
- **Active substance(s): daclatasvir**
- **Pharmaceutical form: film coated tablet**
- **Route of administration: oral use**
- **Strengths: 30 and 60 mg**

2. NAME AND CONTACT DETAILS OF THE COMPANY

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3. TARGET POPULATION

Daclatasvir for the use in combination with sofosbuvir +/- ribavirin, for genotype 1 patients that are above 18 years of age and at a high risk of decompensation or death within 12 months if left untreated.

4. CONDITIONS FOR DISTRIBUTION

Treatment with daclatasvir should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

5. CONDITIONS OF USE

5.1 Posology

Dosing recommendations

Treatment with daclatasvir will be subject to medical prescription and should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

The recommended dose of daclatasvir is 60 mg in combination with sofosbuvir 400 mg once daily for a duration of 24 weeks[1].

Daclatasvir is to be taken orally with or without food.

Discontinuation of therapy

HCV RNA levels should be monitored during treatment. Discontinuation of therapy is recommended for patients experiencing confirmed virologic breakthrough (greater than 1 log10 increase in HCV RNA from nadir). See section 5.3.

Missed doses

Patients should be instructed that, if they miss a dose of daclastasvir, 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.

Special populations

Renal impairment

No dose adjustment of daclatasvir is required for patients with renal impairment.

Hepatic impairment

No dose adjustment of daclatasvir is required for patients with hepatic impairment.

Older people

No dose adjustment of daclatasvir is required for older patients.

Paediatric population

The safety and efficacy of daclatasvir in children aged below 18 years have not yet been established. No data are available.

[1] While the data to date in study AI444040 indicate that the addition of ribavirin to the daclatasvir/sofosbuvir combination did not impact the efficacy in the populations studied, this data are limited. The addition of ribavirin (1000 mg if <75kg; 1200 mg if >75kg) may be considered.

5.2 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients.

Daclatasvir is contraindicated when combined with medicinal products that strongly induce the cytochrome P450 enzyme 3A (CYP3A) or P-glycoprotein (P-gp) and thus may lead to lower exposure and loss of efficacy of daclatasvir.

These active substances include but are not limited to phenytoin, carbamazepine, phenobarbital, rifampin, dexamethasone, and herbal products as St John's wort (Hypericum perforatum).

5.3 Special warnings and precautions for use

Daclatasvir must not be administered as monotherapy.

Insufficient virologic response

In patients who have an inadequate viral response, treatment should be discontinued (see section 5.1.)

Organ transplant patients

There are limited clinical data available (compassionate use only) on the safety and efficacy of daclatasvir in the treatment of HCV infection in patients who have received a liver transplant or other organ transplant patients.

Decompensated patients

There are no clinical data available on the safety and efficacy of daclatasvir in the treatment of patients with decompensated cirrhosis.

HCV/HIV (human immunodeficiency virus) coinfection

There are no clinical data available on the safety and efficacy of daclatasvir in the treatment of HCV infection in patients who are coinfected with HIV.

HCV/HBV (hepatitis B virus) coinfection

There are no clinical data available on the safety and efficacy of daclatasvir in the treatment of HCV infection in patients who are coinfected with HBV.

Important information about some of the ingredients

Daclatasvir contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

5.4 Interaction with other medicinal products and other forms of interaction

Daclatasvir is a substrate of cytochrome P450 enzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp). Therefore, strong inducers of CYP3A4 or P-gp (eg, carbamazepine, phenobarbital, rifampicin) may decrease the plasma levels and therapeutic effect of daclatasvir (see also Contraindications of concomitant use, below). Strong inhibitors of CYP3A4 or P-gp (eg, amiodarone, clarithromycin, erythromycin, itraconazole, ketoconazole, quinidine, ranolazine, ritonavir) may increase the plasma levels of daclatasvir.

Daclatasvir is also an inhibitor of P-gp and organic anion transporting polypeptide (OATP) 1B1 and 1B3. Administration of daclatasvir may increase systemic exposure to medicinal products that are substrates

of P-gp or OATP 1B or 1B3, which could increase or prolong their therapeutic effect and adverse reactions. Caution should be used if the medicinal product has a narrow therapeutic range. Daclatasvir, in vitro, did not inhibit (IC50 > 40 µM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6. While daclatasvir showed time-dependent inhibition of CYP3A4 and is an inducer of CYP3A4 in vitro, daclatasvir did not have a clinically meaningful effect on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Daclatasvir is a moderate inhibitor of breast cancer resistance protein (BCRP).

Contraindications of concomitant use: Daclatasvir is contraindicated when combined with medicinal products that strongly induce CYP3A4 or P-gp, e.g. phenytoin, carbamazepine, phenobarbital, rifampin, dexamethasone, and herbal products as St John's wort (Hypericum perforatum), and thus may lead to lower exposure and loss of efficacy of daclatasvir.

Other interactions:

In clinical drug-drug interaction studies in non-HCV infected subjects, the plasma concentrations of daclatasvir were increased when coadministered with ketoconazole or atazanavir/ritonavir. Plasma concentrations of daclatasvir were decreased when coadministered with efavirenz. Coadministration with daclatasvir resulted in increased plasma concentrations of digoxin and rosuvastatin.

Concentrations of daclatasvir, ciclosporin or tacrolimus were not impacted when either of the latter where coadministered with the former.

The availability of the 30 mg tablet formulation allows a dose to 30 mg QD in the presence of a strong CYP3A4/P-gp inhibitor and a dose increase to 90 mg QD in the presence of a moderate CYP3A4/P-gp inducer.

5.5 Pregnancy and lactation

Pregnancy and contraception requirements

There are no data from the use of daclatasvir in pregnant women.

Studies of daclatasvir in animals have shown reproductive toxicity.

Daclatasvir is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding

Available pharmacokinetic and toxicological data in animals have shown excretion of daclatasvir and metabolites in milk.

It is not known whether daclatasvir is excreted in human milk. Mothers should be instructed not to breastfeed if they are taking daclatasvir.

Fertility

Available toxicological data in animals have not shown effects of daclatasvir or metabolites on fertility.

No human data on the effect of daclatasvir on fertility are available.

5.6 Incompatibilities

Not applicable.

5.7 Overdose

There has been no clinical experience with overdosage of DCV. Treatment of overdose with DCV should consist of general supportive measures. There is no known specific antidote for overdose with DCV.

5.8 Shelf life

2 years

5.9 Storage conditions

Store below 30°C

5.10 Special precautions for disposal

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

6. OTHER INFORMATION

Summary of relevant pharmacological properties

Mechanism of action

Daclatasvir is an inhibitor of NS5A, a mulitfunctional protein necessary for HCV replication. NS5A is an essential component of HCV replication complex.

Antiviral activity in cell culture

Daclatasvir is a potent inhibitor of HCV genotype 1a and 1b replication in cell-based replicon assays with effective concentration (50% reduction, EC50) values of 0.003-0.020 and 0.001-0.004 nM, respectively. Daclatasvir has broad genotype coverage, with replicon EC50 values of 0.003-1.25 nM for genotypes 3a, 4a, 5a, and 6a, and 0.034-19 nM for genotype 2a as well as 0.020 nM for infectious GT-2a (JFH-1) virus.

Resistance

In cell culture

Substitutions conferring daclatasvir resistance were observed in the N-terminal 100 amino acid region of NS5A in a cell-based replicon system. L31V and Y93H were identified as major resistance substitutions in a cell-based HCV genotype 1b replicon system, while major resistance substitutions M28T, L31V/M, Q30E/H/R, and Y93C/H/N were observed in a HCV genotype 1a replicon system.

Single amino acid substitutions for HCV genotype 1b generally conferred low level resistance (for example, variant Y93H <30-fold), while greater resistance was generally observed with linked substitutions in a cell-based replicon system. In the HCV genotype 1a replicon, higher levels of resistance (up to >10,000-fold) were observed with single amino acid and linked substitutions.

Cross-resistance

HCV replicons expressing daclatasvir-associated resistance substitutions remained fully sensitive to interferon-alfa, cyclosporine, and other anti-HCV agents with different mechanisms of action, such as NS3 protease and NS5B polymerase inhibitors.

Summary of relevant clinical properties

Clinical efficacy and safety

The efficacy and safety of daclatasvir in combination with sofosbuvir, with or without ribavirin, in the treatment of infection with chronic HCV genotype 1, 2, or 3 were evaluated in an open-label randomized study (AI444040) in adults without cirrhosis. The dose of daclatasvir was 60 mg once daily and the dose of sofosbuvir was 400 mg once daily. Among the 167 patients with HCV genotype 1 infection, 126 were treatment naive and 41 had failed previous therapy with a protease inhibitor regimen. All of the 44 patients with HCV genotype 2 or 3 infection were treatment-naive. Treatment duration was 12 weeks for 82 treatment-naive HCV genotype 1 patients, and 24 weeks for the remainder of the study population.

The primary endpoint was HCV RNA <25 IU/mL at week 12 post-treatment (SVR12), which was achieved by 98% patients with HCV genotype 1 across all treatment groups and 91% of those with genotype 2/3. Response was not influenced by HCV subtype (1a/1b), IL28B genotype, or use of ribavirin.

Virologic responses for DCV (60 mg QD)/SOF (with and without ribavirin): All Treated Subjects

Number of subjects(percent) with response (N based on modified-intention to treat [ITT] analysis)									
	Treatment-naïve with GT-1			Treatment naïve with GT-2/3			TVR/BOC Failures with GT-1		
	GT-1a	GT-1b	GT-1	GT-2	GT-3	GT-2/3	GT-1a	GT-1b	GT-1
	N=99	N=27	N=126	N=26	N=18	N=44	N=33	N=8	N=41
Virologic Response									
HCV RNA ,LLOQ, TD or TND									
Week 4	97 (98.0)	27 (100.0)	124 (98.4)	26 (100.0)	18 (100.0)	44 (100.0)	32 (97.0)	8 (100.0)	40 (97.6)
EOTR	99 (100.0)	27 (100.0)	126 (100.0)	26 (100.0)	17 (94.4)	43 (97.7)	33 (100.0)	8 (100.0)	41 (100.0)
SVR4	98 (99.0)	25 (92.6)	123 (97.6)	24 (92.3)	16 (88.9)	40 (90.9)	33 (100.0)	8 (100.0)	41 (100.0)
SVR12	97 (98.0)	17 (100.0)	124 (98.4)	24 (93.2)	16 (88.9)	40 (90.9)	32 (97.0)	8 (100.0)	40 (97.6)[a]
SVR24	95 (96.0)	25 (92.6)	120 (95.2)	25 (96.2)	16 (88.9)	41 (93.2)	NA	NA	NA

[A] One subject has missing HCV RNA at follow-up Week 12
NA: Note that the TVR/BOC failures were last to be enroled in the study, SVR24 results were not available at the time of datatbase lock for the Study AI444040
Abbreviations: BOC; boceprever, DCV:daclatasvir, EOTR: end of treatment response, GT: genotype, HCV:hepatitis Cvirus, ITT: intent to treat, LLOQ:lower limit of quantitation, RNA- ribonucleic acid, SOF: sofosbuvir, SVR4, SVR12, SVR24: sustained virologic response (HCV-RNA <LLOQ, TD or TND) or follow-up Weeks 4, 12 and 24, TD:target detected, TND: target not detected, TVR: telaprevir

Safety data of daclatasvir in combination with sofosbuvir are available from the phase II study AI444040, which included 211 patients (41 with prior protease inhibitor failure). Most adverse events were mild or moderate and did not lead to treatment discontinuation or interruption. The most common adverse events were fatigue, headache, and nausea. Two patients discontinued treatment due to adverse events; both achieved SVR. Patients with concomitant ribavirin therapy tended to have more adverse events, in particular those which have been well described with ribavirin therapy and included a greater decline in haemoglobin, and in some cases required dose reduction of ribavirin.

In study AI444040, grade 3-4 laboratory abnormalities were uncommon, the most frequent of which were low phosphorous and elevated glucose. The mean change in haemoglobin for ribavirin- vs non-ribavirin-containing regimens was -2.2 g/dL vs -0.30 g/dL following 24 weeks of therapy and -2.8 g/dL vs -0.90 g/dL following 12 weeks of therapy. Five patients had their ribavirin dose reduced for anaemia.

DCV (60 mg QD)/SOF Summary of safety- Treated Subjects (AI444040)

	Number (%) of Subjects				
	DCV/SOF with RBV		DCV/SOF without RBV		Total
	12 Weeks (N=41)	24 Weeks (N=49)	12 Weeks (N=41)	24 Weeks (N=80)	N=211
Adverse Events					
SAEs	1 (2.4)	6 (12.2)	1 (2.4)	7 (8.8)	15 (7.1)
AEs leading to discontinuation	0	1 (2.00	0	1(1.3)	2 (0.9)
Grade 3/4 AEs	1 (2.4)	3 (6.1)	1 (2.4)	2 (2.5)	7 (3.3)
Most common AEs (≥ 10% total)					
Fatigue	15 (36.6)	18 (36.7)	16 (39.0)	29 (36.3)	78 (37.0)
Headache	9 (22.0)	18 (36.7)	14 (34.1)	20 (25.0)	61 (28.9)
Nausea	8 (19.5)	11 (22.4)	8 (19.5)	14 (17.5)	41 (19.4)
Arthralgia	3 (7.3)	4 (8.2)	5 (12.2)	9 (11.3)	21 (10.0)
Diarrhoea	4 (9.8)	7 (14.3)	2 (4.9)	8 (10.0)	21 (10.0)
Measured Grade 3 Laboratory abnormalities					
Total subjects[a]	5 (12.2)	5 (10.2)	1 (2.4)	4 (5.0)	15 (7.1)
Haemoglobin	0	1 (2.0)	0	0	1 (0.5)
Lymphocytes	0	1 (2.0)	0	0	1 (0.50
Phosphorus (inorganic)	3 (7.3)	1 (2.0)	0	1 (1.3)	5 (2.4)
Fasting serum glucose (high)[b]	0	1 (2.0)	1 (2.4)	2 (2.5)	4 (1.9)
Serum glucose	0	2 (4.9)	0	1 (1.6)	3 (1,6)
Total cholesterol	1 (2.6)	0	0	1 (1.6)	2 (1.0)
Uric acid	1 (2.4)	0	0	0	1 (0.5)

AEs- adverse events, DCV: daclatasvir, SAEs: serious adverse events, RBV:ribavirin, SOF:sofosbuvir
[a] No Grade 4 values were reported. Two subjects had Grade 3 values for 2 different laboratory parameters; one subject had Grade 3 serum glucose and haemoglobin and the other had Grade 3 fasting serum glucose and serum glucose.
[b] All 4 subjects with a Grade 3 fasting serum glucose had a medical history of diabetes mellitus

Pharmacokinetics

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV.

Absorption

Peak daclatasvir concentrations were generally observed approximately 1 to 2 hours post-dose.

Daclatasvir exposure HCV infected subjects appeared to be lower than those observed in healthy volunteers at repeated doses from 1 to 30 mg, but similar at 60 mg.

In vitro studies indicated that daclatasvir is a substrate of P-gp.

Effect of food on oral absorption

Administration of a high-fat meal reduced C_{max} and AUC by 28% and 23%, respectively. Administration of a light meal did not influence daclatasvir exposure.

Distribution

The in vitro protein binding of daclatasvir was 95.6%.

Biotransformation

In vitro studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 the major CYP isoform responsible for the metabolism. No metabolites circulated at levels more than 5% of the parent concentration.

Elimination

Elimination of daclatasvir occurs mainly through faeces (88%) whereas 7% was recovered in urine predominantly as parent drug**.** Following multiple-dose administration of daclatasvir in HCV-infected subjects, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours.

Special populations

Renal impairment

Renally impaired non-HCV-infected subjects with end-stage renal disease (ESRD) receiving hemodialysis and healthy subjects were administered a single oral dose of daclatasvir 60 mg. Exposure of daclatasvir (AUC) was 26.4% higher in subjects with ESRD relative to healthy subjects while C_{max} was similar

Hepatic impairment

The pharmacokinetics of daclatasvir following a 30 mg single dose were studied in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with unimpaired subjects. The Cmax and AUC of total daclatasvir (free and protein-bound drug) were lower in subjects with hepatic impairment; however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.

Paediatric population

No pharmacokinetic data for daclatasvir in children aged below 18 years are available.

7. CONDITIONS FOR SAFETY MONITORING

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) and (2) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the Member State(s) will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

8. DATE OF CHMP OPINION

21 November 2013