EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Daklinza

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision issued [2] / amended on	Product Information affected [3]	Summary
IA/0034	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	24/07/2019		SmPC	
IG/1059	A.1 - Administrative change - Change in the name and/or address of the MAH	15/02/2019	25/03/2019	SmPC, Labelling and PL	
II/0031	Update of section 5.1 of the SmPC in order to add information on long-term efficacy and drug resistance	14/02/2019	25/03/2019	SmPC and Annex II	The CHMP considered data from a completed follow-up study to assess durability of response for approximately 3 years

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	based on final results from study AI444046, listed as a category 3 study in the RMP. This is a phase 3 non-randomized, open-label, long-term follow-up and observational study of durability of efficacy, resistance and characterization of progression of liver disease in subjects with chronic hepatitis C previously treated with daclatasvir and/or asunaprevir. In addition, the Marketing authorisation holder (MAH) took the opportunity to postpone (from Q2 2021 to Q2 2023) the due date of the safety study AI444427 evaluating recurrence of hepatocellular carcinoma. Annex II is updated in accordance. The RMP version 6.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				after treatment with daclatasvir. Among 258 patients who achieved SVR12 with daclatasvir and sofosbuvir (± ribavirin) with a median duration of post-SVR12 follow-up of 38 months, no relapses occurred (with relapses defined as confirmed or last available HCV RNA ≥ LLOQ). Among 302 patients who achieved SVR12 with daclatasvir + pegIFN/RBV with a median duration of post-SVR12 follow-up of 44 months, 2% (n=6) of patients relapsed. With regards to resistance, emergent daclatasvir resistance-associated substitutions have been shown to persist for 3 years post-treatment and beyond for patients treated with daclatasvir-based regimens.
PSUSA/10295 /201807	Periodic Safety Update EU Single assessment - daclatasvir	17/01/2019	n/a		PRAC Recommendation - maintenance
IAIN/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2018	25/03/2019	SmPC and PL	
II/0028	Update of section 5.1 of the SmPC to include the final results of study ALLY-3C (AI444379), an interventional open-label phase 3 study evaluating daclatasvir and sofobuvir with ribavirin in cirrhotic subjects with genotype 3 chronic hepatitis C infection to demonstrate the sustained virologic response at follow-up Week 12 (SVR12) rate, defined as hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of	14/06/2018	10/12/2018	SmPC and PL	In study ALLY-3C, the combination of daclatasvir, sofosbuvir and ribavirin administered for 24 weeks was evaluated in 78 adults infected with hepatitis C virus (HCV) genotype 3 with compensated cirrhosis; the majority of patients were male (57 [73.1%]); median age was 55 years (range 33 to 70); 88.5% were white; 9.0% were Asian; and 2.6% were American Indian or Alaska native; 54 (69.2%) patients were treatment-naïve and 24 (30.8%) patients were

	quantification (LLOQ) target detected (TD) or target not detected (TND) at follow-up Week 12 in subjects treated with 24 weeks of daclatasvir (DCV) + sofosbuvir (SOF) + ribavirin (RBV) therapy was greater than the historical threshold sustained virologic response (SVR) rate. In addition the MAH took the opportunity to include a new statement regarding the amount of sodium contained in the medicinal product in section 4.4 of the SmPC and section 2 of the Package Leaflet in line with the revised 'Guideline on excipients in the labelling and package leaflet of medicinal products for human use', and to update the contact details of the Bulgarian, Estonian, Hungarian, Icelandic, Latvian, Lithuanian and Romanian local representatives in the Package Leaflet. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				treatment-experienced. The overall median HCV RNA was 6.38 log10 IU/mL; the majority of patients (59%) had IL-28B rs12979860 non-CC genotypes. Seventy-seven (77 [98.7%]) of treated patients in this study were infected with HCV GT 1a, and 1 patient (1.3%) was infected with HCV GT 3b. The SVR12 rates were achieved by 88.5% of patients, including 92.6% of treatment-naïve and 79.2% of treatment-experienced patients. SVR12 rates were consistently high across most subgroups including gender, age, race, baseline HCV RNA, and IL28B genotype. All 3 HCV/HIV co-infected patients achieved SVR12.
IG/0889	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	12/02/2018	n/a		
IB/0027	C.I.7.b - Deletion of - a strength	13/01/2018	10/12/2018	SmPC, Labelling and PL	
PSUSA/10295 /201707	Periodic Safety Update - Single assessment - daclatasvir	11/01/2018	n/a		PRAC Recommendation - maintenance

PSUSA/10295 /201701	Periodic Safety Update EU Single assessment - daclatasvir	06/07/2017	n/a		PRAC Recommendation - maintenance
IB/0025	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	30/05/2017	n/a		
A20/0016	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the European Medicines Agency further to a signal of hepatitis B reactivation in patients co-infected with HBV/HCV and concerns over the recurrence of hepatocellular carcinoma in patients using direct-acting antivirals in the context of interferon-free treatment of chronic hepatitis C. The PRAC was requested to assess the impact thereof on the benefit-risk balance of authorised direct-acting antivirals, namely Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax and to give its opinion on whether the marketing authorisation of these products should be maintained, varied, suspended or revoked.	15/12/2016	23/02/2017	SmPC, Annex II and PL	Please refer to the assessment report: Direct-acting antivirals indicated for treatment of hepatitis C (interferon-free) - EMEA/H/A-20/1438
IB/0023	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/01/2017	18/12/2017	SmPC and PL	
PSUSA/10295 /201607	Periodic Safety Update EU Single assessment - daclatasvir	12/01/2017	n/a		PRAC Recommendation - maintenance

II/0020	Update of section 5.1 of the SmPC to update the current figures on baseline nonstructural protein 5A (NS5A) resistance-associated variants observed in clinical trials with daclastavir in combination with sofosbuvir, based on an integrated analysis of resistance prevalence data. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	23/02/2017	SmPC	The MAH submitted the results from an integrated analysis of resistance prevalence data from all daclatasvir (DCV)/sofosbuvir (SOF) and DCV/pegylated interferon (pegINF)/ribavirine (RBV) studies submitted to support the granting of the Marketing Authorisation for Daklinza. In 9 phase 2/3 studies with daclatasvir in combination with peginterferon alfa + ribavirin or in combination with sofosbuvir +/- ribavirin, the following frequencies of resistance-associated variants (RAVs) were observed at baseline: 7% in genotype 1a infection (M28T, Q30, L31, and/or Y93), 11% in genotype 1b infection (L31 and/or Y93H), 51% in genotype 2 infection (L31M), 8% in genotype 3 infection (Y93H) and 64% in genotype 4 infection (L28 and/or L30). In addition baseline nonstructural protein 5A (NS5A) RAVs (at M28T, Q30, L31, and Y93 for genotype 1a; at L31 and Y93 for genotype 1b) increase the risk for non-response in treatment-naive patients infected with genotype 1a and genotype 1b infection. The impact of baseline NS5A RAVs on cure rates of genotype 4 infection is not apparent. In case of non-response to therapy with daclatasvir + peginterferon alfa + ribavirin, NS5A RAVs generally emerged at failure (139/153 genotype 1a and 49/57 genotype 1b). Finally, in limited numbers of genotype 4-infected patients with non-response, substitutions L28M and L30H/S were detected at failure. Section 5.1 of the SmPC has therefore been updated to reflect the above information.
II/0019	Update of section 4.5 of the SmPC to update the current information on the drug-drug interaction between daclatasvir and the narcotic analgesics buprenorphine and norbuprenorphine following	15/09/2016	23/02/2017	SmPC and PL	Results from part 2 of clinical study AAI444064 showed that buprenorphine and its metabolite norbuprenorphine were slightly increased when co-administered with daclatasvir. However; this was not clinically and statistically significant.

	completion of the part 2 of study AAI444064, a phase I open-label drug-drug interaction study between methadone and daclatasvir, and between buprenorphine/naloxone and daclatasvir. In addition the MAH took the opportunity to update the contact details of the Croatian local representative. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Based on this finding, no dose adjustment of DCV or buprenorphine when buprenorphine/naloxone is co-administered with DCV is warranted. In section 4.5 of the SmPC, the AUC and Cmin values for both buprenorphine and norbuprenorphine have been amended accordingly in the 'interactions and dose recommendations with other medicinal products' table. In addition, the recommendation concerning coadministration has been clarified that, although no dose adjustment of Daklinza or buprenorphine may be required, patients should be monitored for signs of opiate toxicity.
PSUSA/10295 /201601	Periodic Safety Update EU Single assessment - daclatasvir	02/09/2016	n/a		PRAC Recommendation - maintenance
IAIN/0021/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	10/08/2016	n/a		
X/0013	Annex I_2.(c) Change or addition of a new strength/potency	28/04/2016	24/06/2016	SmPC, Labelling and PL	

II/0018/G	This was an application for a group of variations. Submission of two final non-clinical study reports, NCPK 278 and NCPK 293 to evaluate the potential pharmacodynamic and pharmacokinetic interactions between amiodarone and HCV direct acting antivirals (DAAs) including daclatasvir, in order to fulfil MEA 015 and 016 . As a consequence the RMP (version 4) was updated. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/06/2016	n/a		
IB/0017/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation B.II.b.2.a - Change to importation, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	21/04/2016	n/a		

	control/testing takes place				
IA/0014/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	11/02/2016	n/a		
II/0010/G	This was an application for a group of variations. C.I.4 Updates of sections 4.2, 4.4, 4.8, 5.1 and 5.2 based on final results of clinical study AI444216 (ALLY-2): "A Phase 3 Evaluation of Daclatasvir plus Sofosbuvir in Treatment-Naive and Treatment Experienced Chronic Hepatitis C (genotype 1, 2, 3, 4, 5, or 6) Subjects Coinfected with Human Immunodeficiency Virus (HIV)". The Package Leaflet is updated accordingly. C.I.4 Updates of sections 4.2, 4.4, 4.8, 5.1, 5.2 based on the final results of clinical study AI444215 (ALLY-1): "A Phase 3 Evaluation of Daclatasvir, Sofosbuvir, and Ribavirin in Genotype 1-6 Chronic Hepatitis C Infection Subjects with Cirrhosis who may require future liver	19/11/2015	28/01/2016	SmPC, Annex II, Labelling and PL	The applicant submitted the procedures stated below: C.I.4 Updates of sections 4.2, 4.4, 4.8, 5.1, 5.2 based on the final results of clinical study AI444215 (ALLY-1): "A Phase 3 Evaluation of Daclatasvir, Sofosbuvir, and Ribavirin in Genotype 1-6 Chronic Hepatitis C Infection Subjects with Cirrhosis who may require future liver transplant and subjects post-liver transplant". The Package Leaflet is updated accordingly. C.I.4 Updates of sections 4.2, 4.4, 4.8, 5.1 and 5.2 based on final results of clinical study AI444216 (ALLY-2): "A Phase 3 Evaluation of Daclatasvir plus Sofosbuvir in Treatment-Naive and Treatment Experienced Chronic Hepatitis C (genotype 1, 2, 3, 4, 5, or 6) Subjects Coinfected with Human Immunodeficiency Virus (HIV)". The Package Leaflet is updated accordingly.

	transplant and subjects post-liver transplant". The Package Leaflet is updated accordingly. The MAH also took the opportunity to update the PI to the latest QRD template (v 9.1), amend the list of local representatives and correct minor editorial corrections to section 4.5 of the SmPC. The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, labelling, Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				ALLY-1 This is the first dedicated efficacy and safety study of DCV in patients with hepatic decompensation and post-transplant. Patients with cirrhosis (Child Pugh A/B/C; the "cirrhotic cohort") and post-transplant patients (with various degrees of fibrosis including cirrhosis, the "post- transplant cohort") were given 12 weeks of therapy with sofosbuvir + daclatasvir + ribavirin (600mg starting dose). Erythropoiesis-stimulating agents were allowed, but in fact not used in any patient; 1 patient received blood transfusion. Although all genotypes were allowed, the majority of patients had genotype-1 infection. High cure rates were seen in the post-transplant cohort, including patients with F3 (12/13) and F4 (15/16) fibrosis, and in patients with Child Pugh A and B in the cirrhotic cohort. In contrast, in patients with the most advanced liver disease (Child Pugh C, cirrhotic cohort) the relapse rate was high (relapse in 6/14 patients without a liver transplant procedure during study + yet another case where HCV-RNA was still detectable at end of treatment). Potential reasons for the high relapse rate in patients with Child Pugh C cirrhosis were explored. It was shown that daclatasvir exposure (including unbound concentration) was similar in patients with Child Pugh A, B and C cirrhosis. In contrast, the actual ribavirin dosage was lower (CP C<CP B<CP A), with a median dose of only 350 mg/d (calculated by actual dosage given over the 12 weeks period, divided by 84 days). That figure is considerable lower than the dose given in a similar study called SOLAR-1, where sofosbuvir/ledipasvir + ribavirin given for 12 weeks yielded similarly low relapse rates in patients with Child Pugh A-C cirrhosis (median dose

					600 mg/d in subset of patients with Child Pugh C cirrhosis treated for 12 weeks. It was concluded that the low ribavirin dosage de facto administered to the Child Pugh C patients may have been suboptimal. As a consequence of ALLY-1, the recommended treatment duration for patients with Child Pugh C cirrhosis was set to 24 weeks. No deaths were reported in ALLY-1 at the time of the follow-up Week 12 database lock. Two subjects in the cirrhotic cohort died after the follow-up Week 12 visit; both deaths (one due to sepsis and the other due to progressive liver failure) were judged to be unrelated to study therapy by investigator assessment. ALLY-2 The results in ALLY-2 provides, as expected, evidence for similar efficacy outcomes with sofosbuvir + daclatasvir in HIV co-infected patients treated for 12 weeks, as in patients only infected with hepatitis C. Although patients with all genotypes were allowed, numbers of patients with non-1 genotypes were low and not evidently supportive for a treatment recommendation for genotypes 2, 5 or 6. There was no trend for loss of control of HIV suppression. No new or unexpected safety signal was observed. No deaths occurred during therapy. None were reported to have stopped therapy due to an adverse event and there were no clinically relevant trends in grade 3/4 laboratory values.
PSUSA/10295 /201507	Periodic Safety Update EU Single assessment - daclatasvir	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0008/G	This was an application for a group of variations.	24/09/2015	28/01/2016	SmPC and PL	DDI data was presented for daclatasvir given in combination with atazanavir, darunavir and lopinavir boosted with

	C.I.4 Update of sections 4.2, 4.4, 4.5 and 5.1 of the SmPC in order to update the safety information based on the final results of clinical study AI444043 (HIV-HCV co-infection study). The Package Leaflet has been updated accordingly. C.I.4 Update of section 4.5 of the SmPC in order to update the safety and interactions and dose recommendations with other medicinal products information based on the final results of clinical study AI444093. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				ritonavir. This data showed that 60 mg of daclatasvir should be used for darunavir/r and lopinavir/r, and 30 mg in combination with atazanavir/r to mimic the "target exposure" seen with 60 mg without interacting drugs. The applicant would like to extrapolate the DDI data to DRV or ATV combinations with cobicistat or cobicistat as combination with elvitegravir, emtricitabine and tenofovir (Stribild). The effect of DRV/RIT and LPV/RIT was lower than expected and due to the lack of complete data on DCV elimination (biliary excretion), extrapolation to unstudied scenarios are somewhat uncertain. However, both from an efficacy and a safety perspective, available data are indicative that the therapeutic margins of daclatasvir, when given with sofosbuvir, are wide. There is no reason to believe that any difference in exposure, of the magnitude that might reasonably occur when replacing ritonavir with cobicistat, would cause problems. The proposed SPC recommendations are thus supported.
IG/0602	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	11/09/2015	n/a		
PSUSA/10295 /201501	Periodic Safety Update EU Single assessment - daclatasvir	10/09/2015	n/a		PRAC Recommendation - maintenance
II/0004	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC to amend the safety information based on the results from clinical study AI444218 (ALLY-3). In addition the	23/07/2015	08/09/2015	SmPC and PL	The results from clinical study AI444218 (ALLY-3) entitled "A Phase 3 Evaluation of Daclatasvir and Sofosbuvir in Treatment Naïve and Treatment Experienced Subjects with

	MAH has made some minor changes in other sections of the SmPC. The package leaflet has been amended accordingly. The requested variation leads to amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Genotype 3 Chronic Hepatitis C Infection" shown that daclatasvir + sofosbuvir (without ribavirin) given for 12 weeks yields a high cure rate in non-cirrhotic patients regardless of prior treatment status (treatment naïve or prior treatment failure to a regimen that did not include an NS5A inhibitor).
II/0005	Submission of the results from two in vitro studies (NCPK 160 and NCPK 212) conducted to evaluate the involvement of transporters, committed in the Risk Management Plan as post authorisation measure (MEA 011). Based on the results of these studies, sections 4.5 and 5.2 of the Summary of Product Characteristics are being updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/07/2015	28/01/2016	SmPC	Submitted data are two in vitro studies investigating daclatasvir uptake transport into hepatocytes. The data suggest that liver uptake of daclatasvir involves multiple pathways (both active transport and passive diffusion) and that the active liver uptake of daclatasvir is mediated by OCT1 and other unidentified transporters. The sections 4.5 and 5.2 of the SmPC have been amended to reflect the new data.
II/0007/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to amend the safety information based on study results from AI444038 and AI444052 clinical studies. The requested group of variations proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to	23/07/2015	08/09/2015	SmPC	The SmPC has been updated in section 4.8 to amend safety information based on AI444052 and AI444038 study results.

	new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0009	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/06/2015	08/09/2015	SmPC and PL	
II/0002	Update of section 4.5 of the SmPC with the final results from clinical study AI444273. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	08/09/2015	SmPC	
IA/0001	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	03/10/2014	08/09/2015	SmPC	