PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Daklinza (daclatasvir)

This is a summary of the risk management plan (RMP) for Daklinza. The RMP details important risks of Daklinza, how these risks can be minimised, and how more information will be obtained about Daklinza's risks and uncertainties (missing information).

Daklinza's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Daklinza should be used.

I. The medicine and what it is used for

Daklinza is authorised for use in combination therapy with other medicinal products for the treatment of HCV infection in adults (see SmPC for the full indication). It contains daclatasvir (as dihydrochloride) as the active substance and it is given by oral administration.

Further information about the evaluation of Daklinza's benefits can be found in Daklinza's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Daklinza, together with measures to minimise such risks and the proposed studies for learning more about Daklinza's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Daklinza is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Daklinza are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks

can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Daklinza. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Drug-drug Interactions
	HBV reactivation
Important potential risks	Hepatic Toxicity
	Hematologic Toxicity
	Development of Drug Resistance
	Embryo-fetal Development Toxicity
	Cardiac arrhythmia (bradycardia), in particular when daclatasvir is concomitantly used with sofosbuvir plus amiodarone and/or other bradycardic medicines
	Recurrence of HCC
	Emergence of HCC
Missing information	Safety in patients of African Origin
	Safety in subjects in whom drugs with potential for clinically significant DDI may be expected to decrease systemic exposure to DCV
	Safety in patients with previous HCC

II.B Summary of important risks

Important identified risks

Drug-drug Interactions	
Evidence for linking the risk to the medicine	CSRs (AI444005, AI444012, AI444027, AI444032, AI444054, AI444093), Corporate Safety Database
Risk factors and risk groups	Patients receiving DCV and interacting drugs (ketoconazole, boosted HIV protease inhibitors, rifampin, digoxin, rosuvastatin, amiodarone).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4
HBV reactivation	
Evidence for linking the risk to the medicine	Health authority inquiries; BMS corporate safety database and literature.
Risk factors and risk groups	• HBV/HCV co-infected patients not on HBV therapy • Patients with HBs antigen positivity

Important identified risks

	• Patients receiving certain immunosuppressants or chemotherapeutic agents
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4

Important potential risks

Hepatic toxicity	
Evidence for linking the risk to the medicine	Analyses of data from core studies.
Risk factors and risk groups	No relationship to changes in HCV RNA was identified. Risk groups or risk factors are unknown.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8
Hematologic toxicity	
Evidence for linking the risk to the medicine	Analyses of data from core studies.
Risk factors and risk groups	Unknown.
Risk minimisation measures	Routine risk minimisation measures: None.
Development of drug resistance	
Evidence for linking the risk to the medicine	Analyses of data from core studies and European HCV database.
Risk factors and risk groups	Patients who have been treated with a NS5A inhibitor prior to receiving a DCV-containing regimen since baseline NS5A resistance-associated polymorphisms may pre-exist and reduce the efficacy of DCV.
Risk minimisation measures	Routine risk minimisation measures: SmPC includes the warning/precaution that DCV must not be administered as monotherapy. Also, monitoring of HCV RNA levels during treatment is recommended in the SmPC, with discontinuation of therapy recommended for patients treated with DCV and pegIFNα/RBV experiencing confirmed virologic breakthrough (greater than 1 $\log_{10}$ increase in HCV RNA from nadir). Treatment stopping rules are provided for the DCV and pegIFNα/RBV regimen.
Embryo-fetal developmental toxicity	
Evidence for linking the risk to the medicine	Analyses of data from core studies.
Risk factors and risk groups	Pregnant women in first trimester.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.6.
Cardiac arrhythmia (bradyardia), in particular when daclatasvir is concomitantly used with sofosbuvir plus amiodarone and/or other bradycardic medicines	

Important potential risks

Evidence for linking the risk to the medicine	Company safety database.
Risk factors and risk groups	No relationship to changes in HCV RNA was identified. Risk groups or risk factors are unknown. It should be noted that the target population has ongoing liver disease and the use in subjects with decompensated cirrhosis, moderate and severe liver disease, and subjects with hepatic transplant is considered missing safety information.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4.
Recurrence of HCC	
Evidence for linking the risk to the medicine	Corporate safety database; published literature.
Risk factors and risk groups	Safety datasets both internal to BMS and in the peer reviewed literature provide limited information on risk factors for recurrence of HCC in patients receiving HCV DAA therapy including DCV-containing regimens.
Risk minimisation measures	Routine risk minimisation measures: There are currently no risk minimisation measures in place - the risk is still being assessed.
Additional pharmacovigilance activities	Per EMA/PRAC recommendation within HCV DAA Article 20 procedure (EMEA/H/A-20/1438), all HCV DAA MAHs including BMS, will conduct a planned prospective, Annex II post authorisation safety study in a well-defined group of patients based on agreed upon protocol setting out criteria for entry and follow-up on the risk of recurrence of HCC (AI444427; see section II.C of this summary for an overview of the post-authorisation development plan).
Emergence of HCC	
Evidence for linking the risk to the medicine	Corporate safety database; published literature.
Risk factors and risk groups	Patients with cirrhosis are at greater risk for emergent HCC than those without cirrhosis. In addition, patients that do not achieve SVR12 are at greater risk for emergent HCC as compared to those achieving SVR12.
Risk minimisation measures	Routine risk minimisation measures: There are currently no risk minimisation measures in place - the risk is still being assessed.
Additional pharmacovigilance activities	Per EMA/PRAC recommendation within HCV DAA Article 20 procedure (EMEA/H/A-20/1438), all HCV DAA MAHs including BMS, will conduct a feasibility assessment on the use of existing data sources for studying the relative risk between IFN-free and IFN-containing HCV DAA on the incidence of emergence of HCC in cirrhotic patients without a history of HCC. If the use of existing data sources proves infeasible, BMS will consider a prospective safety study to further understand the risk for emergence of HCC. See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information

Safety in patients of African Origin	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 5.1 and 5.2
Safety in subjects in whom drugs with potential for clinically significant DDI may be expected to decrease systemic exposure to DCV	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3, 4.4, and 4.5
Safety in patients with previous HCC	
Risk minimisation measures	Routine risk minimisation measures: There are currently no risk minimisation measures in place - the risk is still being assessed
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Per EMA/PRAC recommendation within HCV DAA Article 20 procedure (EMEA/H/A-20/1438), all HCV DAA MAHs including BMS will conduct a planned prospective, Annex II post authorisation safety study in a well-defined group of patients based on agreed upon protocol setting out criteria for entry and follow-up on the risk of recurrence of HCC (AI444427; see section II.C of this summary for an overview of the post-authorisation development plan).

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Category 1 and 2 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
AI444427 (DAA-PASS): A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy	DAA therapy exposure during routine clinical care of HCV-infected patients with successfully treated HCC, in the prospective DAA-PASS cohort.

II.C.2 Other studies in post-authorisation development plan

Category 3 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
Planned:	
AI444428 (DAA PASS): A study to evaluate the risk of emergence of hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C	Evaluate the potential risk of emergence of hepatocellular carcinoma following direct-acting antiviral treatment in hepatitis C virus infected patients with compensated cirrhosis without a history of hepatocellular carcinoma.