▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. 1.NAME OF THE MEDICINAL PRODUCT, QUALITATIVE AND QUANTITATIVE COMPOSITION Daklinza 30 mg film-coated tablets. Each film-coated tablet contains daclatasvir dihydrochloride equivalent to 30 mg daclatasvir. Excipient(s) with known effect: Each 30-mg film-coated tablet contains 58 mg of lactose (as anhydrous). Daklinza 60 mg film-coated tablets. Each film-coated tablet contains daclatasvir dihydrochloride equivalent to 60 mg daclatasvir. Excipient(s) with known effect: Each 60-mg film-coated tablet contains 116 mg of lactose (as anhydrous).For the full list of excipients, see section 6.1 of SmPC. **4.CLINICAL PARTICULARS 4.1 THERAPEUTIC INDICATIONS** Daklinza is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults (see sections 4.2, 4.4 and 5.1 of SmPC). For HCV genotype specific activity, see sections 4.4 and 5.1 of SmPC. **4.2 POSOLOGY AND METHOD OF ADMINISTRATION** Treatment with Daklinza should be initiated and monitored by a physician experienced in the management of chronic hepatitis C. Posology The recommended dose of Daklinza is 60 mg once daily, to be taken orally with or without meals. Daklinza must be administered in combination with other medicinal products. The Summary of Product Characteristics for the other medicinal products in the regimen should also be consulted before initiation of therapy with Daklinza.Recommended regimens and treatment duration are provided in Table 1 below (see sections 4.4 and 5.1 of SmPC):

Table 1: Recommended regimens and treatment duration for Daklinza combination therapy

HCV genotype and patient population*	**Treatment**	**Duration**
Genotype 1 or 4 without cirrhosis	Daklinza + sofosbuvir	12 weeks Consider prolongation of treatment to 24 weeks for patients with prior treatment including a NS3/4A protease inhibitor (see sections 4.4 and 5.1 of SmPC)
Genotype 1 or 4 with compensated cirrhosis	Daklinza + sofosbuvir	24 weeks Shortening treatment to 12 weeks may be considered for previously untreated patients with cirrhosis and positive prognostic factors such as IL28B CC genotype and/or low baseline viral load. Consider adding ribavirin for patients with very advanced liver disease or with other negative prognostic factors such as prior treatment experience.
Genotype 3 without cirrhosis	Daklinza + sofosbuvir	12 weeks
Genotype 3 with cirrhosis	Daklinza + sofosbuvir +/- ribavirin	24 weeks Ribavirin may be added based on clinical assessment of an individual patient

Table 1: Recommended regimens and treatment duration for Daklinza combination therapy

HCV genotype and patient population*	Treatment	Duration
Genotype 4	Daklinza + peginterferon alfa + ribavirin	24 weeks of Daklinza in combination with 24-48 weeks of peginterferon alfa and ribavirin. If the patient has HCV RNA undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks. If the patient achieves HCV RNA undetectable, but not at both treatment weeks 4 and 12, Daklinza should be discontinued at 24 weeks and peginterferon alfa and ribavirin continued for a total duration of 48 weeks.

The dose of ribavirin, when combined with Daklinza, is weight-based (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively). *Dose modification, interruption and discontinuation* Dose modification of Daklinza to manage adverse reactions is not recommended. If treatment interruption of components in the regimen is necessary because of adverse reactions, Daklinza must not be given as monotherapy. There are no virologic treatment stopping rules that apply to the combination of Daklinza with sofosbuvir.*Treatment discontinuation in patients with inadequate on-treatment virologic response during treatment with Daklinza, peginterferon alfa and ribavirin* 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. The HCV RNA thresholds that trigger discontinuation of treatment (i.e. treatment stopping rules) are presented in Table 2.

Table 2: Treatment stopping rules in patients receiving Daklinza in combination with peginterferon alfa and ribavirin with inadequate on-treatment virologic response

HCV RNA	Action
Treatment week 4: >1000 IU/ml	Discontinue Daklinza, peginterferon alfa and ribavirin
Treatment week 12: ≥25 IU/ml	Discontinue Daklinza, peginterferon alfa and ribavirin
Treatment week 24: ≥25 IU/ml	Discontinue peginterferon alfa and ribavirin (treatment with Daklinza is complete at week 24)

Dose recommendation for concomitant medicines *Strong inhibitors of cytochrome P450 enzyme 3A4 (CYP3A4)* The dose of Daklinza should be reduced to 30 mg once daily when coadministered with strong inhibitors of CYP3A4. *Moderate inducers of CYP3A4* The dose of Daklinza should be increased to 90 mg once daily when coadministered with moderate inducers of CYP3A4. See section 4.5 of SmPC. *Missed doses* Patients should be instructed that, if they miss a dose of Daklinza, 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 *Elderly* No dose adjustment of Daklinza is required for patients aged ≥65 years (see sections 4.4 and 5.2 of SmPC). *Renal impairment* No dose adjustment of Daklinza is required for patients with any degree of renal

impairment (see section 5.2 of SmPC). *Hepatic impairment* No dose adjustment of Daklinza is required for patients with mild (Child-Pugh A, score 5-6), moderate (Child-Pugh B, score 7-9) or severe (Child-Pugh C, score ≥10) hepatic impairment. Daklinza has not been studied in patients with decompensated cirrhosis (see sections 4.4 and 5.2 of SmPC). *Paediatric population* The safety and efficacy of Daklinza in children and adolescents aged below 18 years have not yet been established. No data are available. Method of administration Daklinza is to be taken orally with or without meals. Patients should be instructed to swallow the tablet whole. The film-coated tablet should not be chewed or crushed due the unpleasant taste of the active substance. **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC.Coadministration with medicinal products that strongly induce cytochrome P450 3A4 (CYP3A4) and P-glycoprotein transporter (P-gp) and thus may lead to lower exposure and loss of efficacy of Daklinza. These active substances include but are not limited to phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, systemic dexamethasone, and the herbal product St John's wort *(Hypericum perforatum)*. **4.8 Undesirable effects** Summary of the safety profile The overall safety profile of daclatasvir is based on data from 1899 patients with chronic HCV infection who received Daklinza once daily either in combination with sofosbuvir with or without ribavirin (n=363, pooled data) or in combination with peginterferon alfa and ribavirin (n=1536, pooled data) from a total of 12 clinical trials. *Daklinza in combination with sofosbuvir* The most frequently reported adverse reactions were fatigue, headache, and nausea. No Grade 3 or 4 adverse reactions were reported. Two patients discontinued for adverse events, which were considered unrelated to study therapy. *Daklinza in combination with peginterferon alfa and ribavirin* The most frequently reported adverse reactions were fatigue, headache, pruritus, anaemia, influenza-like illness, nausea, insomnia, neutropenia, asthenia, rash, decreased appetite, dry skin, alopecia, pyrexia, myalgia, irritability, cough, diarrhoea, dyspnoea and arthralgia. The most frequently reported adverse reactions of at least Grade 3 severity (frequency of 1% or greater) were neutropenia, anaemia, lymphopenia and thrombocytopenia. The safety profile of daclatasvir in combination with peginterferon alfa and ribavirin was similar to that seen with peginterferon alfa and ribavirin alone, including among patients with cirrhosis. Overview list of adverse reactions Adverse reactions are listed by regimen, system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. **Adverse reactions in clinical trials** *Daklinza + sofosbuvir + ribavirin (N=90)* Blood and lymphatic system disorders: very common: anaemia/ Metabolism and nutrition disorders: common: decreased appetite/ Psychiatric disorders: common: insomnia,irritability/ Nervous system disorders: very common: headache – common: dizziness, migraine/ Vascular disorders:common: hot flush/ Respiratory, thoracic and mediastinal disorders: very common: cough – common: dyspnoea, dyspnoea exertional, nasal congestion/ Gastrointestinal disorders:very common: nausea – common: diarrhoea, vomiting, abdominal pain, gastrooesophageal reflux disease, constipation, dry mouth, flatulence /Skin and subcutaneous tissue disorders:very common: pruritus-common: dry skin, alopecia, rash/ Musculoskeletal and connective tissue disorders: common: arthralgia, myalgia/ General disorders and administration site conditions:very common: fatigue. *Daklinza + sofosbuvir (N=273)*Psychiatric disorders: common: insomnia/Nervous system disorders: very common: headache – common: dizziness, migraine/Gastrointestinal disorders: common: nausea, diarrhea, abdominal pain/ Musculoskeletal and connective tissue disorders: common: arthralgia, myalgia/ General disorders and administration site conditions:very common: fatigue. *Laboratory abnormalities* In the clinical trial of Daklinza in combination with sofosbuvir with or without ribavirin, one patient had a Grade 3 hemoglobin decrease; this patient was in a ribavirin treatment group. Laboratory abnormalities among patients treated with Daklinza, peginterferon alfa and ribavirin were similar to those among patients treated with placebo, peginterferon and ribavirin. Description of selected adverse reactions *Cardiac arrhythmias* Cases of severe bradycardia and heart block have been observed when Daklinza is used in combination with sofosbuvir and concomitant amiodarone and/or other drugs that lower heart rate (see sections 4.4 and 4.5 of SmPC).Paediatric population The safety and efficacy of Daklinza in children and adolescents aged <18 years have not yet been established. No data are available.Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Federal Agency for Medicines and Health Products. Division Vigilance Eurostation II Place Victor Horta 40, boîte 40. B-1060 Brussels, Site internet: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be. 7.MARKETING AUTHORISATION HOLDER **Bristol-Myers Squibb Pharma EEIG Uxbridge Business Park Sanderson**

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