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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206-843
Supporting document/s:	S001, S002, S003
Applicant's letter date:	August 5, 2015
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Product:	Daclatasvir
Indication:	Anti-Hepatitis C Virus
Applicant:	Bristol-Myers Squibb Company (BMS)
Review Division:	Division of Antiviral Products
Reviewer:	L. Peyton Myers, PhD
Supervisor/Team Leader:	Hanan Ghantous, PhD, DABT
Division Director:	Debra Birnkrant, MD
Project Manager:	Sohail Mosaddegh, Pharm.D.

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1 Executive Summary

1.1 Introduction

Daclatasvir (DCV, 60-mg), is a Hepatitis C Virus (HCV) nonstructural protein 5A (NS5A) inhibitor proposed for the treatment of HCV. DCV inhibits HCV NS5A protein with high affinity. DCV is proposed to be used with other anti-HCV drug products. DCV is a novel compound.

1.3 Recommendations

1.3.1 Approvability

There are no nonclinical pharmacology and toxicology (P/T) issues which would preclude the approval of DCV 60 mg tablets.

This P/T review is primarily for label changes, including PLLR format changes.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Suggested Pharmacology/Toxicology labeling:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No adequate human data are available to determine whether or not DAKLINZA poses a risk to pregnancy outcomes. In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of daclatasvir during organogenesis at doses that produced exposures up to 6 and 22 times, respectively, the recommended human dose (RHD) of 60 mg of DAKLINZA. However, embryofetal toxicity was observed in rats and rabbits at maternally toxic doses that produced exposures of 33 and 98 times the human exposure, respectively, at the RHD of 60 mg of DAKLINZA [see Data]. In rat pre- and postnatal developmental studies, no developmental toxicity was observed at maternal systemic exposure (AUC) to daclatasvir approximately 3.6 times higher than the RHD of DAKLINZA.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

If DAKLINZA and sofosbuvir are administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.
Data

Animal Data

Daclatasvir was administered orally to pregnant rats at doses of 0, 50, 200, or 1000 mg/kg/day on gestation days 6 to 15. Maternal toxicity (mortality, adverse clinical signs, body-weight losses, and reduced food consumption) was noted at doses of 200 and 1000 mg/kg/day. In the offspring, malformations of the fetal brain, skull, eyes, ears, nose, lip, palate, or limbs were observed at doses of 200 and 1000 mg/kg. The dose of 1000 mg/kg was associated with profound embryolethality and lower fetal body weight. No malformations were noted at 50 mg/kg/day. Systemic exposure (AUC) at 50 mg/kg/day in pregnant females was 6 times higher than exposures at the RHD.

In rabbits, daclatasvir was initially administered at doses of 0, 40, 200, or 750 mg/kg/day during the gestation days 7 to 19. Daclatasvir dosing was modified due to vehicle toxicity during the study to doses of 20, 99, and 370 mg/kg/day, respectively. Maternal toxicity was noted at doses of 200/99 and 750/370 mg/kg/day with adverse clinical signs and severe reductions in body weight and food consumption. Mortality and euthanasia occurred in multiple dams at 750/370 mg/kg/day. At 200/99 mg/kg/day, fetal effects included increased embryofetal lethality, reduced fetal body weights, and increased incidences of fetal malformations of the ribs as well as head and skull. No malformations were noted in rabbits at 40/20 mg/kg/day. Systemic exposures (AUC) at 40/20 mg/kg/day were 22 times higher than exposures at the RHD.

In a pre- and postnatal developmental study, daclatasvir was administered orally at 0, 25, 50, or 100 mg/kg/day from gestation day 6 to lactation day 20. At 100 mg/kg/day maternal toxicity included mortality and dystocia; developmental toxicity included slight reductions in offspring viability in the perinatal and neonatal periods and reductions in birth weight that persisted into adulthood. There was neither maternal nor developmental toxicity at doses up to 50 mg/kg/day. Systemic exposures (AUC) at this dose were 3.6 times higher than the RHD.

8.2 Lactation

Risk Summary

It is not known whether DAKLINZA is present in in human milk, affects human milk production, or has effects on the breastfed infant. Daclatasvir was present in the milk of lactating rats (see Data).

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for DAKLINZA and any potential adverse effects on the breastfed child from DAKLINZA or from the underlying maternal condition.

If DAKLINZA is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

Data

Milk concentrations of daclatasvir were evaluated on lactation day 10 as part of the rat pre- and postnatal development study (see Data in 8.1). Daclatasvir was present in rat milk with concentrations 1.7 to 2 times maternal plasma levels.

8.3 Females and Males of Reproductive Potential

If DAKLINZA and sofosbuvir are administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

A 2-year carcinogenicity study in Sprague Dawley rats and a 6-month study in transgenic (Tg rasH2) mice were conducted with daclatasvir. In the 2-year study in rats, no drug-related increase in tumor incidence was observed at doses up to 50 mg/kg/day (both sexes). Daclatasvir exposures at these doses were approximately 6-fold (males and females) the human systemic exposure at the therapeutic daily dose of DAKLINZA. In transgenic mice no drug-related increase in tumor incidence was observed at doses of 300 mg/kg/day (both sexes).

Daclatasvir was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity (Ames) assays, mammalian mutation assays in Chinese hamster ovary cells, or in an in vivo oral micronucleus study in rats.
If DAKLINZA and sofosbuvir are administered in a regimen containing ribavirin, the information for ribavirin on carcinogenesis and mutagenesis also applies to this combination regimen [see prescribing information for ribavirin].

Impairment of Fertility

Daclatasvir had no effects on fertility in female rats at any dose tested. Daclatasvir exposures at these doses in females were approximately 24-fold the human systemic exposure at the therapeutic daily dose of DAKLINZA. In male rats, effects on reproductive endpoints at 200 mg/kg/day included reduced prostate/seminal vesicle weights, minimally increased dysmorphic sperm, as well as increased mean pre-implantation loss in litters sired by treated males. Daclatasvir exposures at the 200 mg/kg/day dose in males were approximately 26-fold the human systemic exposure at the therapeutic daily dose of DAKLINZA. Exposures at 50 mg/kg/day in males produced no notable effects and was 4.7-fold the exposure in humans at the recommended daily dose of DAKLINZA.

If DAKLINZA and sofosbuvir are administered with ribavirin, the information for ribavirin on impairment of fertility also applies to this combination regimen [see prescribing information for ribavirin].

2 Drug Information

2.1 Drug

CAS Registry Number
1214735-16-6
Generic Name
Daclatasvir, DCV
Code Name
BMS-790052
Chemical Name
[[1,1'-Biphenyl]-4,4'-diylbis[1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl[(1S)-1-(1-methylethyl)-2- oxo-2,1-ethanediyl]]]biscarbamic acid, dimethyl ester, dihydrochloride
Molecular Formula/Molecular Weight
$C_{40}H_{50}N_8O_6.2HCl$ / (b) (4) (free base 738.88)
Structure or Biochemical Description

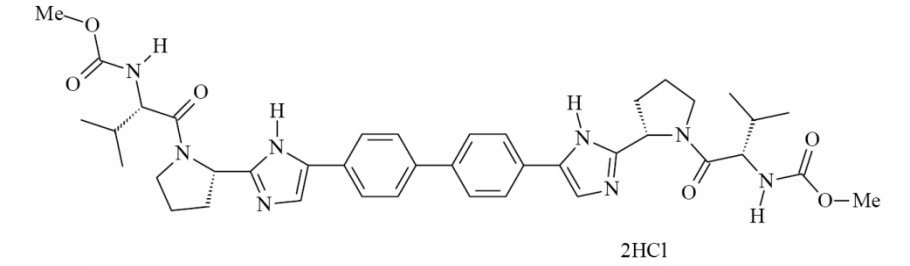

Figure 1 - Structure of DCV

Pharmacologic Class
Hepatitis C Virus NS5A inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 79599 – primary IND for DCV

2.7 Regulatory Background

DCV was evaluated in clinical trials under IND 79599. DCV was previously approved under this NDA.

DCV label is being updated to conform to the PLLR format changes.

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/s/

LAINE P MYERS
01/26/2016

HANAN N GHANTOUS
01/27/2016