

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208624Orig1s000

PHARMACOLOGY REVIEW(S)

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

**PHARMACOLOGY/TOXICOLOGY
MEMORANDUM TO NDA 208624 FILE: LABELING REVIEW**

Application number: 208624
Applicant's letter date: 9/28/15
CDER stamp date: 9/28/15
Product: Viekira XR; Dasabuvir, ombitasvir, paritaprevir and ritonavir (200 mg/8.33 mg/50 mg/33.33 mg) fixed-dose combination tablets
Indication: Treatment of patients with G1 chronic HCV infection, including those with compensated cirrhosis.
Applicant: AbbVie, Inc.
Review Division: DAVP
Reviewer: Ilona G. Bebenek, Ph.D., DABT
Supervisor/Team Leader: Hanan Ghantous, Ph.D., DABT
Division Director: Debra Birnkrant, M.D.
Project Manager: Suzanne Strayhorn, M.S.

With this current submission, AbbVie proposes a new formulation of the components that constituted Viekira Pak - to a new single dosage tablet form, referenced as the '3QD tablet'. This new formulation is proposed, to allow for a once daily dosing regimen and AbbVie intends to replace Viekira Pak™ following approval of this new NDA. AbbVie has utilized the approved Viekira Pak labeling information (USPI and Medication Guide) as a template for their proposed draft labeling submitted to this new NDA. As a result, the current proposed draft labeling (submitted February 17, 2016 and May 02, 2016), largely mirrors the approved package insert for Viekira Pak™ (NDA 206619/S009).

The differences between the current submission label for Viekira XR-NDA 208624 and approved label for Viekira Pak NDA 206619/S9 are under sections 8 and 13. The order in which the individual drug data is presented under those sections is different. Under Viekira Pak, the order of presentation is the following: ombitasvir, paritaprevir/ritonavir and dasabuvir. In the current submission (Viekira XR label), the order of presentation is the following: dasabuvir, ombitasvir and paritaprevir/ritonavir. Both sections 8 and 13 in the Viekira XR label largely mirror sections 8 and 13 in the Viekira Pak approved label.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

If VIEKIRA XR is 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.

No adequate human data are available to establish whether or not VIEKIRA XR poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when the components of VIEKIRA XR were administered separately during organogenesis and lactation. During organogenesis, the exposures were up to 28 and 4 times (mice and rabbits, respectively; ombitasvir), 8 and 98 times (mice and rats, respectively; paritaprevir, ritonavir), and 24 and 6 times (rats and rabbits, respectively; dasabuvir) exposures at the recommended clinical dose of VIEKIRA XR. In rodent pre/postnatal developmental studies, maternal systemic exposures (AUC) to ombitasvir, paritaprevir and dasabuvir were approximately 25, 17 and 44 times, respectively, the exposure in humans at the recommended clinical dose [see Data].

The background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

Data

Animal data

Dasabuvir

Dasabuvir was administered orally to pregnant rats (0, 60, 300 and 800 mg/kg/day) and rabbits (0, 100, 200 or 400 mg/kg/day) during the period of organogenesis (on GD 6 to 17 and GD 7 to 20, respectively). There were no test article-related embryofetal effects (malformations or fetal toxicity) at any dose level in either species. The highest systemic exposure of dasabuvir was 24-times higher (rats) and 6-times higher (rabbits) than the exposures in humans at the recommended clinical dose.

In a pre- and postnatal developmental study in rats, dasabuvir was administered orally at 0, 50, 200, or 800 mg/kg/day from GD 7 to lactation day 21. There were no treatment-related effects at maternal exposures 44-times higher than exposures in humans at the recommended clinical dose.

Ombitasvir

Ombitasvir was administered orally to pregnant mice (0, 15, 50, or 150 mg/kg/day) and rabbits (0, 10 or 60 mg/kg/day) during the period of organogenesis (on gestation days (GD) 6 to 15, and GD 7 to 19, respectively). There were no ombitasvir-related embryofetal effects (malformations or fetal toxicity) at any dose level in either species. The systemic exposures at the highest doses were 28-times higher (mice) and 4-times higher (rabbits) than the exposures in humans at the recommended clinical dose.

In a pre- and postnatal developmental study in mice, ombitasvir was administered orally at 0, 10, 40, or 200 mg/kg/day from GD 6 to lactation day 20. There were no ombitasvir-related effects at maternal exposures 25-times higher than exposures in humans at the recommended clinical dose.

The major human metabolites of ombitasvir, M29 and M36, were tested in pregnant mice during the period of organogenesis from GD 6 to 15. M29 was administered orally at doses of 0, 1, 2.5 or 4.5 mg/kg/day. M36 was dosed orally at doses 1.5, 3, or 6 mg/kg/day. In both cases, there were no treatment related embryofetal effects (malformations or fetal toxicity) at any dose level. The highest doses produced exposures approximately 26-times higher than the exposures in humans at the recommended clinical dose.

Paritaprevir/ritonavir

Paritaprevir/ritonavir was administered orally to pregnant rats (0/0, 30/15, 100/15, 450/45 mg/kg/day) and mice (0/0, 30/30, 100/30, or 300/30 mg/kg/day) during the period of organogenesis (on GD 6 to 17, and GD 6 to 15, respectively). There were no test article-related embryofetal effects (malformations or fetal toxicity) at any dose level in either species. The highest systemic exposure of paritaprevir was 8-times higher (rats) and 98-times higher (mice) than the exposures in humans at the recommended clinical dose.

In a pre- and postnatal developmental study in rats, paritaprevir/ritonavir were administered orally at 0/0, 6/30, 30/30, or 300/30 mg/kg/day from GD 7 to lactation day 20. There were no treatment related effects at maternal exposures 17-times higher than exposures in humans at the recommended clinical dose.

8.2 Lactation

RiskSummary

It is not known whether VIEKIRA XR and its metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13, and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups [see *Data*].

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

If VIEKIRA XR is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use during lactation.

Data

Animal Data

Dasabuvir

No effects of dasabuvir on growth and postnatal development were observed in nursing pups at the highest dose tested (800 mg/kg/day) in rats. Maternal systemic exposure (AUC) to dasabuvir was approximately 44 times the exposure in humans at the recommended clinical dose. Although not measured directly, dasabuvir was likely present in the milk of lactating rats in this study, since systemic exposure was observed in nursing pups on post-natal day 14 (approximately 14% of maternal exposure).

When dasabuvir was administered to lactating rats (5 mg/kg on post-partum day 10 to 11), milk exposure (AUC) was 2 times higher than that in plasma, with unchanged parent drug (78%) accounting for the majority of drug-related material in milk.

Ombitasvir

No effects of ombitasvir on growth and postnatal development were observed in nursing pups at the highest dose tested (200 mg/kg/day) in mice. Maternal systemic exposure (AUC) to ombitasvir was approximately 25 times the exposure in humans at the recommended clinical dose. Although not measured directly, ombitasvir was likely present in the milk of lactating mice in this study, since systemic exposure was observed in nursing pups on post-natal day 21 (approximately 16% of maternal exposure).

When ombitasvir was administered to lactating rats (5 mg/kg on post-partum day 10 to 11), milk exposure (AUC) was 4 times higher than that in plasma, with unchanged parent drug (91%) accounting for the majority of drug-related material in milk.

Paritaprevir/ritonavir

No effects of paritaprevir/ritonavir on growth and postnatal development were observed in nursing pups at the highest dose tested (300/30 mg/kg/day) in rats. Maternal systemic exposure (AUC) to paritaprevir was approximately 17 times the exposure in humans at the recommended clinical dose. Although not measured directly, paritaprevir was likely present in the milk of lactating rats at the high dose in this study, since systemic exposure was observed in nursing pups on post-natal day 15 (approximately 0.3 % of maternal exposure).

When paritaprevir/ritonavir was administered to lactating rats (30/15 mg/kg on post-partum day 10 to 11), milk exposure (AUC) was half that in plasma, with the hydrolysis product M13 (84%) and unchanged parent drug (16%) accounting for all paritaprevir-related material in milk.

8.3 Females and Males of Reproductive Potential

If VIEKIRA XR is 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

Dasabuvir

Dasabuvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (2000 mg per kg per day). Similarly, dasabuvir was not carcinogenic in a 2-

year rat study up to the highest dose tested (800 mg per kg per day), resulting in dasabuvir exposures approximately 19-fold higher than those in humans at 500 mg.

Dasabuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assays.

Ombitasvir

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (150 mg per kg per day). Similarly, ombitasvir was not carcinogenic in a 2-year rat study up to the highest dose tested (30 mg per kg per day), resulting in ombitasvir exposures approximately 16-fold higher than those in humans at 25 mg.

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Paritaprevir, ritonavir

Paritaprevir, ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (300/30 mg per kg per day). Similarly, paritaprevir, ritonavir was not carcinogenic in a 2-year rat study up to the highest dose tested (300/30 mg per kg per day), resulting in paritaprevir exposures approximately 9-fold higher than those in humans at 150 mg.

Paritaprevir was positive in an *in vitro* chromosome aberration test using human lymphocytes. Paritaprevir was negative in a bacterial mutation assay, and in two *in vivo* genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests).

If VIEKIRA XR is administered with ribavirin, refer to the prescribing information for ribavirin for information on carcinogenesis, and mutagenesis.

Impairment of Fertility

Dasabuvir

Dasabuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 800 mg per kg per day. Dasabuvir exposures at this dose were approximately 16-fold the exposure in humans at the recommended clinical dose.

Ombitasvir

Ombitasvir had no effects on embryo-fetal viability or on fertility when evaluated in mice up to the highest dose of 200 mg per kg per day. Ombitasvir exposures at this dose were approximately 25-fold the exposure in humans at the recommended clinical dose.

Paritaprevir, ritonavir

Paritaprevir, ritonavir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 300/30 mg per kg per day. Paritaprevir exposures at this dose were approximately 2- to 5-fold the exposure in humans at the recommended clinical dose.

If VIEKIRA XR is administered with ribavirin, refer to the prescribing information for ribavirin for information on Impairment of Fertility.

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/s/

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06/22/2016

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06/23/2016