CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208984Orig1s000
022128Orig1s017

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/BLA REVIEW AND EVALUATION

Application number:	208-984
Supporting document:	001
Applicant's letter date:	May 6, 2016
CDER stamp date:	May 6, 2016
Product:	Maraviroc, Selzentry®, UK-427,857
Indication:	Treatment of HIV-1 infection
Applicant:	ViiV Healthcare Company Five Moore Drive Research Triangle Park, NC 27709
Review Division:	DAVP
Reviewer:	Pritam Verma, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D.
Division Director:	Debra Birnkrant, M.D.
Project Manager:	Andrew Gentles

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208-984 are owned by ViiV Healthcare Company or are data for which ViiV Healthcare Company has obtained a written right of reference. Any information or data necessary for approval of NDA 208-984 that ViiV Healthcare Company does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208-984.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY.....3

1.1 INTRODUCTION…….3

1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS……....3
1.3 RECOMMENDATIONS…….3
1.3.3 LABELING……..3
2.1 DRUG.....5
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS……..6
2.3 PROPOSED CLINCAL POPULATION AND DOSING REGIMEN……6
2.4 REGULATORY BACKGROUND:……....6

3 STUDIES SUBMITTED:……... 6

11 INTEGRATED SUMMARY AND SAFETY EVALUATION……7

1 Executive Summary

1.1 Introduction

SELZENTRY (Maraviroc) is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1. NDA 208984 supports expansion of labeling to reflect new clinical data from pediatric patients as young as 2 years of age and approval of a new oral solution (20 mg/mL) dosage form. The proposed indication for maraviroc solution is in combination with other antiretroviral medicinal products only in CCR5-tropic HIV-1 patients.

A comprehensive review of the nonclinical studies for maraviroc has been performed under NDA 22128.

1.2 Brief Discussion of Nonclinical Findings

To support clinical use, the nonclinical toxicity profile of maraviroc was characterized in an extensive battery of in vitro and in vivo studies including carcinogenicity studies in rats and mice. The pivotal toxicology studies supporting the safety of maraviroc were appropriately designed and conducted in compliance with Good Laboratory Practice (GLP) regulations. A toxicology program was completed involving repeat-dose studies, which identified toxicological end-points, together with doses of maraviroc without adverse effects. Maraviroc had no adverse effects on fertility other than a statistically significant increase in pre-implantation loss at the high dose in rats, and has no teratogenic potential. Similarly maraviroc was shown not to be mutagenic or clastogenic in appropriate genetic toxicology assays. Carcinogenicity studies in rats and transgenic mice indicated no carcinogenic potential for humans. In conclusion, the results of extensive nonclinical toxicology and pharmacokinetic evaluation programs support the proposed use of maraviroc in humans.

1.3 Recommendations

1.3.1 Approvability

It is recommend that SELZENTRY oral solution be approved

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The reviewer’s recommendation for the nonclinical portion of the drug label is included below:

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SELZENTRY during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Limited data on the use of SELZENTRY during pregnancy from the APR and case reports are not sufficient to inform a drug-associated risk of birth defects and miscarriage. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with maraviroc. During organogenesis in the rat and rabbit, systemic exposures (AUC) to maraviroc were approximately 20 times (rats) and 5 times (rabbits) the exposure in humans at the recommended 300 mg twice-daily dose. In the rat pre- and post-natal development study, maternal systemic exposure (AUC) to maraviroc was approximately 14 times the exposure in humans at the recommended 300 mg twice-daily dose *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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: Maraviroc was administered orally to pregnant rats (up to 1,000 mg per kg per day) and rabbits (up to 75 mg per kg per day) on gestation Days 6 to 17 and 7 to 19, respectively. No adverse effects on embryo-fetal development were observed at these dose levels, resulting in exposures (AUC) approximately 20 times (rats) and 5 times (rabbits) higher than human exposures at the recommended daily dose. In the rat pre- and post-natal development study, maraviroc was administered orally at up to 1,000 mg per kg per day on gestation Day 6 to lactation/post-partum Day 20, with development of the offspring (including fertility and reproductive performance) unaffected by maternal administration of maraviroc at an exposure (AUC) approximately 14 times higher than human exposure at the recommended daily dose.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

There are no data on the presence of maraviroc in human milk, the effects on the breastfed infant, or the effects on milk production. When administered to lactating rats, maraviroc was present in milk *[see Data]*. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving SELZENTRY.

Data

Maraviroc (and related metabolites) was excreted into the milk of lactating rats following a single oral dose of maraviroc (100 mg per kg) on lactation Day 12, with a maximal milk concentration achieved one hour post-administration at a milk concentration approximately 2.5 times that of maternal plasma concentrations.

13. NONCLINCIAL TOXICOLOTY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term oral carcinogenicity studies of maraviroc were carried out in rasH2 transgenic mice (6 months) and in rats for up to 96 weeks (females) and 104 weeks (males). No drug-related increases in tumor incidence were found in mice at 1,500 mg per kg per day and in male and female rats at 900 mg per kg per day. The highest exposures in rats were approximately 11 times those observed in humans at the therapeutic dose of 300 mg twice daily for the treatment of HIV-1 infection.

Mutagenesis

Maraviroc was not genotoxic in the reverse mutation bacterial test (Ames test in Salmonella and E. coli), a chromosome aberration test in human lymphocytes, and rat bone marrow micronucleus test.

Impairment of Fertility

Maraviroc did not impair mating or fertility of male or female rats and did not affect sperm of treated male rats at approximately 20-fold higher exposures (AUC) than in humans given the recommended 300-mg twice-daily dose.

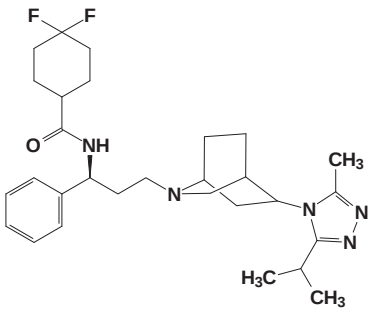
Drug Information

2.1 Drug:

Trade name: SELZENTRY^{R}
Generic name: Maraviroc
Code name: UK-427,857
Chemical name: 4,4-difluoro-N-{1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-

triazol 4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}
cyclohexanecarboxamide
CAS registry number: 376348-65-1
Molecular formula: $C_{29}H_{41}F_2N_5O$
Molecular weight: 513.7
Melting Point: 193.5 degrees C
Solubility: >25.6 mg/ml in 0.1 M HCl
Description: White solid of uniform appearance

Structure:



2.2 Relevant INDs, NDAs and DMFs: 65,229, 22,128

2.6 Proposed Clinical Population and Dosing Regimen

NDA 208984 supports expansion of labeling to reflect new clinical data from pediatric patients as young as 2 years of age and approval of a new oral solution (20 mg/mL) dosage form.

2.7 Regulatory Background

This application is being submitted as a New Drug Application (NDA) for Selzentry (maraviroc) Oral Solution (20 mg/ml). The pre-assigned NDA number is 208984. Reference is made to ViiV Healthcare's NDA 22128 for Selzentry (maraviroc) Tablets 150 mg and 300 mg Tablets originally approved on August 6, 2007. The sponsor has incorporated NDA 22128 by full reference. Reference is also made to ViiV Healthcare's supplemental NDA, submitted on the date of this letter (22128; Sequence 340), seeking approval of two lower strength tablets (25 mg and 75 mg), which we are also incorporating by reference.

3. Studies Submitted

All nonclinical studies for current NDA is cross-referenced to the original NDA and IND and no additional nonclinical toxicology information is included in this submission package. Refer to applicable sections of IND 65,229 and NDA 22128.

II Integrated Summary and Safety Evaluation

The following table is showing estimated safety margins for maraviroc based on AUCss when comparing animal NOAELs to human exposures

Maraviroc exposures in multiple dose toxicity studies in animals vs humans

Study No.	Study, species & route	Dose (mg/kg/day)	NOEL/NOAEL (mg/kg/day)	AUC (µg*hr/ml) at NOEL/NOAEL	Multiples of human exposures (x)
1.	2-wk mice, po	20			
		200	200	13.25	4
		1000			
		2000			
2.	2-wk dogs, po	10	Not identified	2.2	1
		50			
		250			
3.	1- month mice, po	200	200	33.65	9
		500			
		750			
4.	1- month rats, po	100	100	7.4	2
		300			
		1500			
5.	1-month dogs, po	5	5	6.02	2
		50			
		150			
6.	1-month monkeys, po	100	100	4.21	1
		200			
		400			
		800			
7.	3-month mice, po	200	200	13	4
		500			
		750			
8.	6- month rats, po	30			
		100	100	20	6
		300			
		900			
9.	6-month dogs, po	5	5	2.42	1
		15			
		40			
10.	9-month monkeys, po	30			
		120	120	6.6	2
		400			

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRITAM S VERMA
10/12/2016

HANAN N GHANTOUS
10/12/2016
I concur with Dr. Verma on the recommendation to approve Selzentry.

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	22128/S-017
Supporting document:	663
Applicant's letter date:	May 6, 2016
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Indication:	Treatment of HIV-1 infection
Applicant:	ViiV Healthcare Company Five Moore Drive Research Triangle Park, NC 27709
Review Division:	DAVP
Reviewer:	Pritam Verma, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D.
Division Director:	Debra Birnkrant, M.D.
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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY.....3

1.1 INTRODUCTION…….3

1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS……....3
1.3 RECOMMENDATIONS…….3
1.3.3 LABELING……..3
2.1 DRUG.....5
2.2 RELEVANT INDS, NDAS, BLAS AND DMFS……..6
2.3 PROPOSED CLINCAL POPULATION AND DOSING REGIMEN……6
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1 Executive Summary

1.1 Introduction

SELZENTRY (Maraviroc) is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1. NDA 22128 S-17 supports expansion of labeling to reflect new clinical data from pediatric patients as young as 2 years of age and approval of a new tablet strengths (25 mg and 75 mg). The recommended dose is based on patient weight and on concomitant medications because of maraviroc drug interactions.

A comprehensive review of the nonclinical studies for maraviroc has been performed under NDA 22128.

1.2 Brief Discussion of Nonclinical Findings

To support clinical use, the nonclinical toxicity profile of maraviroc was characterized in an extensive battery of in vitro and in vivo studies including carcinogenicity studies in rats and mice. The pivotal toxicology studies supporting the safety of maraviroc were appropriately designed and conducted in compliance with Good Laboratory Practice (GLP) regulations. A toxicology program was completed involving repeat-dose studies, which identified toxicological end-points, together with doses of maraviroc without adverse effects. Maraviroc had no adverse effects on fertility other than a statistically significant increase in pre-implantation loss at the high dose in rats, and has no teratogenic potential. Similarly maraviroc was shown not to be mutagenic or clastogenic in appropriate genetic toxicology assays. Carcinogenicity studies in rats and transgenic mice indicated no carcinogenic potential for humans. In conclusion, the results of extensive nonclinical toxicology and pharmacokinetic evaluation programs support the proposed use of maraviroc in humans.

1.3 Recommendations

1.3.1 Approvability

It is recommended that SELZENTRY new tablet strengths be approved.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The reviewer's recommendation for the nonclinical portion of the drug label is included below:

8. USE IN SPECIFIC POPULATIONS

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8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

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13. NONCLINCIAL TOXICOLOTY

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Mutagenesis

Maraviroc was not genotoxic in the reverse mutation bacterial test (Ames test in Salmonella and E. coli), a chromosome aberration test in human lymphocytes, and rat bone marrow micronucleus test.

Impairment of Fertility

Maraviroc did not impair mating or fertility of male or female rats and did not affect sperm of treated male rats at approximately 20-fold higher exposures (AUC) than in humans given the recommended 300-mg twice-daily dose.

Drug Information

2.1 Drug:

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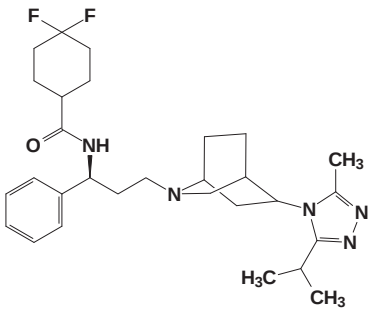
Generic name: Maraviroc
Code name: UK-427,857
Chemical name: 4,4-difluoro-N-{1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-

triazol 4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}
cyclohexanecarboxamide
CAS registry number: 376348-65-1
Molecular formula: $C_{29}H_{41}F_2N_5O$
Molecular weight: 513.7
Melting Point: 193.5 degrees C
Solubility: >25.6 mg/ml in 0.1 M HCl
Description: White solid of uniform appearance

Structure:



2.2 Relevant INDs, NDAs and DMFs: 65,229, 22,128

2.6 Proposed Clinical Population and Dosing Regimen

NDA 22128/S-17 supports expansion of labeling to reflect new clinical data from pediatric patients as young as 2 years of age and approval of new tablet strengths.

2.7 Regulatory Background

This application is being submitted as a NDA 22128 S-17 for Selzentry (maraviroc) new tablet strengths. Reference is made to ViiV Healthcare's NDA 22128 for Selzentry (maraviroc) Tablets 150 mg and 300 mg Tablets originally approved on August 6, 2007. The sponsor has incorporated NDA 22128 by full reference. Reference is also made to ViiV Healthcare's supplemental NDA, submitted on the date of this letter (22128; Sequence 663), seeking approval of two lower strength tablets (25 mg and 75 mg), which we are also incorporating by reference.

3. Studies Submitted

All nonclinical studies for current NDA is cross-referenced to the original NDA and IND and no additional nonclinical toxicology information is included in this submission package. Refer to applicable sections of IND 65,229 and NDA 22128.

II Integrated Summary and Safety Evaluation

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		400			
		800			
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		100	100	20	6
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		40			
10.	9-month monkeys, po	30			
		120	120	6.6	2
		400			

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/s/

PRITAM S VERMA
10/12/2016

HANAN N GHANTOUS
10/12/2016
I concur with Dr. Verma's recommendation that SELZENTRY new tablet strengths be approved.