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APPLICATION NUMBER:

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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:	206088
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Applicant's letter date:	09/23/2013
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Product:	OTEZLA (apremilast) tablets
Indication:	Psoriasis
Applicant:	Celgene Corporation
Review Division:	Dermatology and Dental Products
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1 Executive Summary

1.1 Introduction

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. It has been recently approved for the treatment of psoriatic arthritis under NDA 205437 (same sponsor). The sponsor intends to develop apremilast for the treatment of psoriasis as well. The same dosage was proposed for apremilast in this NDA as that approved under NDA 205437 (maximum recommended human dose of 30 mg BID).

1.2 Brief Discussion of Nonclinical Findings

Apremilast is a PDE4 inhibitor. PDE4 inhibition results in increased intracellular cAMP levels, affecting numerous cellular functions in PDE4 responsive cells. It has been demonstrated that CC-10004 alters many pro- and anti-inflammatory mediators in in vitro and/or in vivo conditions. Apremilast showed certain efficacy in a human NK cell driven animal model of psoriasis. The sponsor proposed that the ability of CC-10004 to modulate levels of pro- and anti-inflammatory mediators will provide therapeutic benefit in psoriasis patients.

In safety pharmacology studies, no neurological effects were noted in mice at a single oral dose of 500 mg/kg CC-10004. Minor neurological effects including lacrimation, ptosis and apathy were seen at higher doses. CC-10004 inhibited the hERG channel current only partially and only at very high concentrations. CC-10004 induced a dose-related increase in dP/dt_{max} and heart rate in anaesthetized dogs. Corrected QT interval was not affected in this study. Peak inspiratory flow and peak expiratory flow were both increased in this study. The results suggest that CC-10004 does not have a high risk for producing QT prolongation.

PK studies were conducted in mice, rats, rabbits, and monkeys. Oral bioavailability of CC-10004 was ~20-33% in mice, ~78% in monkeys, ~12% in male rats and ~63% in female rats, and < 1% in rabbits. Due to pronounced sex differences in PK and toxicity profiles of CC-10004, rat was not used in pivotal repeat dose toxicology studies. Due to the poor oral bioavailability of CC-10004 in rabbits, monkey was used as an alternative species in reproductive toxicology studies. There were no unique metabolites identified in humans that were not identified in animal species used in toxicology studies.

Pivotal repeat dose toxicology studies were conducted in mice and monkeys. Arteritis was a major toxicity finding noted in mouse studies. It occurred in a variety of tissues and appeared to be associated with a general inflammatory reaction. The arteritis was described as acute inflammatory cell infiltrate in all layers of the vessel wall, perivascular edema and hemorrhage, disruption of the elastic lamina, occasional minor areas of necrosis and areas of fibrosis. Other findings included neutrophil count increase, centrilobular liver hypertrophy, hyperkeratosis and gastritis of the stomach, hemopoiesis in the spleen, and lymphoid hyperplasia in lymph nodes and thymus. In a

chronic (6-month) oral toxicity study in mice, oral doses of 0, 10, 100 and 1000 mg/kg/day CC-10004 were tested. Treatment-related mortality was noted at mid and high doses. Histopathological findings noted in mid and high dose animals included: lesions in the heart that involved inflammation of the aortic root or around the cardiac arteries and in the myocardium, vascular inflammation, hematoma formation and centrilobular hepatocellular hypertrophy of the liver. The NOAEL was identified as 10 mg/kg/day.

The toxicity profile of CC-10004 was different in monkeys. Monkey was not susceptible to CC-10004 induced toxicity. In a chronic (12-month) toxicity study, oral doses up to 600 mg/kg/day were tested and no significant toxicity was observed. The NOAEL was identified as 600 mg/kg/day.

In genetic toxicology studies, apremilast tested negative in the Ames assay, an in vitro chromosome aberration assay of human peripheral blood lymphocytes, and an in vivo mouse micronucleus assay. There is no significant concern for its genotoxic potential.

Two 2-year oral carcinogenicity studies were conducted with apremilast (in mice and rats, respectively). No evidence of apremilast-induced tumors was observed in mice at oral doses up to 1000 mg/kg/day or in rats at oral doses up to 20 mg/kg/day in males and 3 mg/kg/day in females, respectively. There is no significant concern for its carcinogenic potential.

In a fertility study of male mice, apremilast at oral (gavage) doses up to 50 mg/kg/day produced no effects on male fertility. In a fertility study of female mice, at doses > 20 mg/kg/day, estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses ≥ 20 mg/kg/day also had increased incidences of early post-implantation losses. There was no significant effect of apremilast at 10 mg/kg/day.

In embryo-fetal development studies in mice, no teratogenic findings attributed to apremilast were observed. However, there was an increase in post-implantation loss at doses ≥ 20 mg/kg/day. At doses ≥ 20 mg/kg/day skeletal variations were noted, which included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at 10 mg/kg/day.

In an embryo-fetal developmental study in cynomolgus monkeys, a dose-related increase in spontaneous abortions was noted at doses ≥ 50 mg/kg/day. No abortifacient effects were observed at 20 mg/kg/day. Although there was no evidence for a teratogenic effect, aborted fetuses were not examined.

In a pre- and post-natal developmental study in mice, dystocia, reduced viability, and reduced birth weights occurred at doses ≥ 80 mg/kg/day. No adverse effects occurred at 10 mg/kg/day. There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring

at doses up to 300 mg/kg/day. Apremilast was detected in the milk of lactating mice at levels ~1.5 times the simultaneous plasma level at 1 and 6 hr postdose.

In the approved OTEZLA label under NDA 205437, the pregnancy category for apremilast is designated as C. A pregnancy exposure registry is established for OTEZLA.

CC-10004 in an ethanol:propylene glycol vehicle did not cause dermal irritation in rabbits or guinea pigs, but was classified as a weak sensitizer in a dermal sensitization study in guinea pigs. CC-10004 did not show phototoxic potential in a neutral red uptake assay.

This NDA is approvable from a pharmacology/toxicology perspective. No post-marketing requirement is recommended for this NDA.

1.3 Recommendations

1.3.1 Approvability

NDA 206088 for OTEZLA (apremilast) tablets is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the OTEZLA label.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the OTEZLA label reproduced below. The pharmacologic class designation for OTEZLA is phosphodieasterase 4 inhibitor. This is an established pharmacologic class.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
OTEZLA, an inhibitor of phosphodieasterase 4 (PDE4), is indicated for the treatment of adult patients with

- active psoriatic arthritis (1.1)
- moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (1.2).

8.1 Pregnancy

Pregnancy Category C:

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women

exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972.

Risk Summary

Adequate and well-controlled studies with OTEZLA have not been conducted in pregnant women. In animal embryo-fetal development studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the (b) (4) recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. In mice, there were no apremilast induced malformations up to exposures 4.0-times the MRHD. The incidences of malformations and pregnancy loss in human pregnancies have not been established for OTEZLA. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Labor or delivery
The effects of OTEZLA on labor and delivery in pregnant women are unknown. In mice, dystocia was noted at doses corresponding to ≥ 4.0-times the MRHD (on an AUC basis at doses ≥ 80 mg/kg/day) of apremilast.

Animal Data
Monkey embryo-fetal development: In an embryo-fetal developmental study, cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during weeks 3 to 4 of dosing in the first trimester, at doses approximately 2.1-times the MRHD and greater (on an AUC basis at doses ≥ 50 mg/kg/day). No abortifacient effects were observed at a dose approximately 1.4-times the MRHD (on an AUC basis at a dose of 20 mg/kg/day). Although, there was no evidence for a teratogenic effect at doses of 20 mg/kg/day and greater when examined at day 100, aborted fetuses were not examined.

Mouse embryo-fetal development: In an embryo-fetal development study, apremilast was administered at (b) (4) of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation day 6 through 15). In a combined fertility and embryo-fetal development study, apremilast was administered at (b) (4) of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of 2.3-times the MRHD and greater (≥ 20 mg/kg/day). At doses of ≥ 20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately 1.3-times

the MRHD (10 mg/kg/day).

Mouse pre- and postnatal development: In a pre- and postnatal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from day 6 of gestation through day 20 of lactation, with weaning on day 21. Dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to ≥ 4.0-times the MRHD (on an AUC basis at doses ≥ 80 mg/kg/day). No adverse effects occurred at a dose 1.3-times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to 7.5-times the MRHD (on an AUC basis at a dose of 300 mg/kg/day).

8.3 Nursing Mothers

It is not known whether OTEZLA or its metabolites are present in human milk; however apremilast was detected in milk of lactating mice. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman.

12.1 Mechanism of Action

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, (b) (4) The specific mechanism(s) by which apremilast exerts its therapeutic action in psoriatic arthritis patients and psoriasis patients is not well defined.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors was observed in mice at oral doses up to 8.8-times the MRHD on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively).

Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay.

In a fertility study of male mice, apremilast at oral (b) (4) up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral (b) (4) of 10, 20, 40, or 80 mg/kg/day. At (b) (4) ≥ 1.8-times the MRHD (≥ 20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at (b) (4) of 20 mg/kg/day and greater also had increased incidences of early postimplantation losses. There was no effect of apremilast approximately 1.0-times the MRHD (10 mg/kg/day).

2 Drug Information

2.1 Drug

CAS Registry Number: 608141-41-9

Generic Name: Apremilast

Code Name: CC-10004

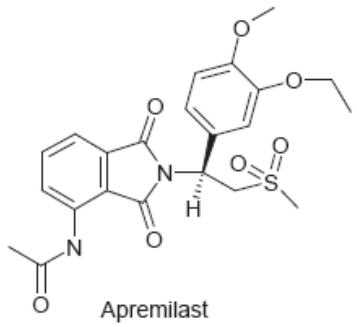
Chemical Name:

(b) (4)

Molecular Formula/Molecular Weight:

$C_{22}H_{24}N_2O_7S$ / 460.5

Structure Description:



Pharmacologic Class: Phosphodiesterase type IV (PDE4) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 205437	OTEZLA, psoriatic arthritis, DPARP, approved on 03/21/2014
IND 70270	Apremilast, psoriasis, DDDP, opened on 07/29/2004, active
IND 101761	Apremilast, (b) (4) and psoriatic arthritis, DPARP, opened on 12/16/2008, active

2.3 Drug Formulation

The composition of OTEZLA (apremilast) tablets (10, 20, and 30 mg) is listed in the following table.

			Tablet Strength (mg/tablet)		
Component	**Function**	**Quality Standard**	**10 mg**	**20 mg**	**30 mg**
Apremilast	Active ingredient	In-house	10.0	20.0	30.0
Microcrystalline Cellulose	(b) (4)				
Lactose Monohydrate					
Croscarmellose Sodium					
Magnesium Stearate					
(b) (4)					
(b) (4)					

(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients. All the inactive ingredients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products.

2.5 Comments on Impurities/Degradants of Concern

There are no toxicological concerns regarding the impurities or degradants at the levels detected (refer to nonclinical review for NDA 205437, dated 11/20/2013).

2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: Adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Dosing regimen: The recommended maintenance oral dosage is 30 mg BID (60 mg/day). A 5-day initial dosage titration is proposed to reduce the gastrointestinal symptoms associated with initial therapy. The proposed maintenance dosage and titration schedule are the same as those approved under NDA 205437. The dosage titration schedule is shown in the table below:

Day 1	Day2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

2.7 Regulatory Background

The apremilast development program for psoriasis was initiated under IND 70270 (opened on 07/29/2004). An EOP2 meeting was conducted on 03/12/2010, a Pre-Phase 3 meeting was conducted on 12/08/2010, and a Pre-NDA meeting was conducted on 05/15/2013. Apremilast was also being developed for the treatment of psoriatic arthritis, rheumatoid arthritis (b) (4). NDA 205437 (corresponding to IND 101761) was submitted to DPARP on 03/21/2013 (indication: psoriatic arthritis) and was approved on 03/21/2014. Subsequently NDA 206088 (corresponding to IND 70270) was submitted to DDDP on 09/23/2013 (indication: psoriasis).

During nonclinical development, issues regarding the interpretation of reproductive and developmental toxicology studies were addressed. Upon review of the monkey embryofetal developmental study, reviewers for IND 70270 and IND 101761 concurred that there was an inadequate assessment of teratogenicity due to fetal demise and abortion (refer to nonclinical review for IND 101761, dated 12/06/2010). However, after consultation with Dr. Abby Jacobs, it was agreed that this could be addressed through labeling and repeat of the study was unnecessary (refer to nonclinical review for NDA 205437, dated 11/20/2013). During the review process for NDA 205437, a labeling meeting was conducted on 01/27/2014 to address the labeling issues on reproductive and developmental toxicity. Nonclinical teams for NDA 205437 and NDA 206088, and Drs. Paul Brown and Timothy McGovern attended the meeting. It was agreed that the embryofetal development study in monkeys was acceptable. The recommended labeling documented in the nonclinical review for NDA 205437 (dated 11/20/2013) was further revised. (b) (4)

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology studies:

1. Effects of CC-2001, CC-4047, CC-5013, CC-11006, CC-10004, CC-11050, CC 401, and (b) (4) on Carrageenan-induced hyperalgesia in rats (Study# 1270RC35.001)
2. Anti-inflammatory activities of the novel PDE4 inhibitor CC-10004 against human leukocytes in vitro (Study# 5042-107)
3. Screening of iMiDs® and PDE4 inhibitor compounds for anti-angiogenic activity in the human umbilical cord vessel ring assay (Study# 5127-132)
4. Effect of IMiDs, PDE4 inhibitors, and tubulin inhibitors on COX-2 expression and PGE2 production by human PBMC (Study# 5197-130)
5. Effect of the PDE4 inhibitors CC-10004, (b) (4) (cilomilast), CC-11050 and (b) (4) (roflumilast), and the IMiD CC-5013 on IL-6 production by human, rat, mouse and monkey whole blood stimulated with LPS in vitro (Study# 5265-117)
6. PDE4 and TNF-α inhibitory activity of CC-10004 metabolites M1, M2, M3 (Racemate), M5 (Racemate), and M7 (Study# 5275-179)
7. Effect of the PDE4i's CC-10004 and CC-11050 on proliferation and AKT phosphorylation in HUVEC (Study# 5279-153)
8. Effect of IMiDs and PDE4 inhibitors on lung fibroblast proliferation and TGF-beta production (Study# 5299-083)
9. The effect of thalidomide and IMiDs including lenalidomide (CC-5013), CC-11006, and CC-10015, and the PDE4 inhibitors CC-10004 and CC-11050 on thromboxane B2 and prostacyclin production in endothelial cell/platelet co-cultures (Study# 5299-148)
10. PDE4 and TNF-alpha inhibitory activity of CC10004 metabolite M12 ([^{14}C]O desmethyl glucuronide) (Study# 5347-137)
11. Investigation of the anti-angiogenic potential of CC-10004 and CC-11050 in endothelial cells (Study# 5387-08)
12. Multiple cytokine profiling for PDE4 inhibitors CC-10004, (b) (4), CC-11050, (b) (4) in LPS-stimulated human PBMCs (Study# 5424-11)
13. Phosphodiesterase 4 and Tumor Necrosis Factor-alpha inhibitory activity of CC-10004 S-isomer metabolites M3, M12 (synthesized), M16, and M17 (Study# 5424-75)
14. Inhibition of Ultraviolet Light B induced TNF-alpha production by Thalidomide (CC-2001), Pomalidomide (CC-4047), Lenalidomide (CC-5013), Apremilast (CC-10004), CC-10015, CC-11006, CC-11050, CC-13097, CC-15965, (b) (4), CC-16057, (b) (4) in primary human neonatal epidermal keratinocytes and primary mouse epidermal keratinocytes (Study# 5448-74)

15. Multiple cytokine profiling for Phosphodiesterase Type 4 inhibitors CC-10004 and CC-11050 in anti-CD3 monoclonal antibody stimulated human T cells (Study# 5478-159)
16. Effect of PDE4 inhibitors and IMiDs on human dermal fibroblast proliferation and PAI-1 production (Study# 5570-044)
17. Effect of phosphodiesterase 4 inhibitors, CC-11050 and apremilast (CC-10004) on interferon-alpha and tumor necrosis factor-alpha production by CpG-A oligodeoxynucleotide stimulated human peripheral blood mononuclear cells and plasmacytoid dendritic cells (Study# 5638-35)
18. Phosphodiesterase 4 and tumor necrosis factor-alpha inhibitory activity of CC-10004 (apremilast) metabolite M14 (N-deacetylated O-desmethylated glucuronide) (Study# 5638-96)
19. In vitro effects of CC-10004 and CC-11050 alone and in combination with anti-rheumatic agents on synovial markers in primary chondrocytes and rheumatoid arthritis synovial fibroblasts (Study# 5673-140)
20. Effect of Apremilast on transcriptional regulation and gene expression in monocytes, peripheral blood mononuclear cells, Jurkat T cell leukemia and THP-1 monocytic leukemia cells (Study# 7600-011)
21. Effect of apremilast on cytokine and chemokine production in LPS-stimulated human whole blood using the TruCulture System (Study# 7600-043)
22. Effect of Apremilast on primary human osteoclasts and osteoblasts in vitro (Study# 7645-001)
23. In vitro pharmacology and ADME-Tox diversity profile + CYP450 + HERG- study of four compounds (Study# 8611)
24. Anti-apoptotic effects of phosphodiesterase 4 inhibitors apremilast and CC-11050 to Ultraviolet Light B exposure in SKH-1 female mouse skin (Study# AP2599)
25. Effect of pretreatment with CC-11050 or CC-10004 on LPS-induced serum TNF-alpha in female CD rats (Study# AP279R, AP284R, AP291R)
26. Effect of pretreatment with CC-11050, CC-10004, (b) (4) or (b) (4) on Carrageenan-induced paw edema in the rat (Study# AP343R)
27. Effect of pretreatment with CC-11050, CC-10004 or (b) (4) on neutrophil infiltration and TNF-alpha production in the airpouch of rats (Study# AP352R)
28. Effect of PDE4 inhibitors CC-11050, CC-10004, (b) (4) on a mouse model of collagen-induced arthritis (Study# AP707R, AP830R)
29. In vitro pharmacology study of CC0010004 (Study# 100005452, sponsor ref# CC-10004-ET-151)
30. Evaluation of anti-arthritic activity in the mAb/LPS-induced experimental murine arthritogenic model (Study# CLG-001-EM)
31. Evaluation of anti-arthritic activity in the mAb/LPS-induced experimental murine arthritogenic model (Study# CLG-001-EM Histology)
32. Evaluation of anti-arthritic activity in the mAb/LPS-induced experimental murine arthritogenic model (Study# CLG-002-EM)
33. Effects of Enbrel and/or CC-10004 in antibody-induced arthritis in mice (Study# CLG-002-EM Histology)
34. Evaluation of anti-arthritic activity in the mAb/LPS-induced experimental murine arthritogenic model (Study# CLG-003-EM)

35. Histological analysis of hind limb ankle joints from murine arthritogenic model (Study# CLG-003-EM Histology)
36. Therapeutic effect of CC-10004 and CC-11050 in collagen-induced arthritis (Study# KIR-P03604)
37. Evaluation of CC-10004 in the T and B cell transfer model in mice (Study# MDCG-5)
38. Phosphodiesterase (PDE) inhibitor assays enzymatic study of 4 compounds (Study# PDE 0801)
39. Phosphodiesterase (PDE) inhibitor assays: enzymatic study of six compounds from Celgene Corp (Study# PDE4-1001)
40. SelectScreen biochemical kinase profiling of CC-220 and CC-10004 (Apremilast) (Study# SSBK8217_23649)
41. CC-11050 and CC-10004 in treatment of psoriasiform (Study# TECH1102006)
42. Mouse Type II collagen arthritis model (Study# WEL 01-027)
43. Therapeutic index of SelCIDs in ferret lung neutrophilia and emesis model (Study# 121401)
44. CC-10004 (apremilast) does not bind human cereblon (Study# 2744-121)
45. Effect of PDE4 inhibitors CC-11050 and apremilast and JNK inhibitor CC-930 on Type I interferon pathophysiology in cellular models of cutaneous lupus (Study# 3252-910)
46. Anti-proliferative activity of CC-4047, CC-5013, CC-5079, and CC-10004 against the non-Hodgkins B lymphoma cell line Farage in vitro (Study# 5196-141-155)
47. Evaluation of two test items, CC-10004 and CC-11050 in the air pouch gout-like inflammation model in mice (Study# MD-2-2-005-1168)
48. Evaluation of two test items, CC-10004 and CC-11050 in the gout-like peritonitis model in mice (Study# MD-2-2-005-1169)
49. Effect of CC-10004 +/- 16,16-diemthyl PGE2 and CC-4047 on cell adhesion molecules in TNF-α stimulated human umbilical vein endothelial cells (HUVEC) (Study# 5226-086-5265-012)
50. Effects of phosphodiesterase 4 inhibitors CC-10004 and CC-11050 in combination with cyclosporine a, methotrexate and etanercept on rheumatoid arthritis and psoriasis associated cytokine production in stimulated t cells (Study# 5589-97)
51. Evaluation of the effect of apremilast treatment on the TH-17 cells in the murine model of collagen induced arthritis (Study# MD-3-2-005-1220)
52. Evaluation of CC-10004 in combination with methotrexate and indomethacin in the collagen-induced arthritis model (Study# MDCG-6)
53. Treatment of psoriasiform with methotrexate in combination with apremilast (Study# TECH10282009)

Safety Pharmacology studies:

54. CC-10004: Gastrointestinal motility assessment following oral administration to male CD-1 mice (Study# (b) (4)-553077, sponsor ref# CC-10004-TOX-1171)
55. Effects of CC-10004 on cloned herg channels expressed in mammalian cells (Study# 031206.DFN)

56. Cardiovascular and respiratory effects in the anaesthetised dog following intravenous administration (Study# 1398/264-D6146)
57. CC-10004: Effects on general activity and behaviour in the mouse following oral administration (Study# 1398/443)

Pharmacokinetic Studies:

58. Validation of an analytical procedure for the determination of (b) (4) in monkey plasma (heparin anticoagulant) using solid phase extraction for sample preparation and liquid chromatography with mass spectrometric detection (study# 1398/135-D0142)
59. Validation of an analytical procedure for the determination of (b) (4) in rat plasma (heparin anticoagulant) using solid phase extraction for sample preparation and liquid chromatography with mass spectrometric detection (Study# 1398/136-D0142)
60. Validation of an analytical procedure for the determination of (b) (4) (b) (4) CC-10004 and (b) (4) in mouse plasma (heparin) using solid phase extraction and liquid chromatography with tandem mass spectrometric detection (Study# 1398/251-D0142)
61. Validation of an analytical procedure for the determination of CC-10004 in rabbit plasma (heparin) using solid phase extraction and liquid chromatography with tandem mass spectrometric detection (Study# 1398/347-D0142)
62. Investigation into the storage stability of CC-10004 in rabbit plasma using solid phase extraction and liquid chromatography with tandem mass spectrometric detection (Study# 1398/362-D0142)
63. Determination of CC-10004 and (b) (4) in heparinized mouse plasma by LC/MS/MS (Study# CC-10004-DMPK-001)
64. Determination of CC-10004 and (b) (4) in heparinized rat plasma by LC/MS/MS (Study# CC-10004-DMPK-002)
65. Determination of CC-10004 and (b) (4) in heparinized monkey plasma by LC/MS/MS (Study# CC-10004-DMPK-003)
66. Determination of CC-10004 and (b) (4) in heparinized rabbit plasma by LC/MS/MS (Study# CC-10004-DMPK-004)
67. Determination of CC-16085 (Desmethyl CC-10004) and CC-16166 (Desmethyl CC-10004 Glucuronide) in heparinized CDI mouse plasma by LC/MS/MS (Study# CC-10004-DMPK-016)
68. Determination of CC-16085 (Desmethyl CC-10004) and CC-16166 (Desmethyl CC-10004 Glucuronide) in heparinized monkey plasma by LC/MS/MS (Study# CC-10004-DMPK-025)
69. Validation of a method for the determination of CC-10004 in lithium heparinized mouse plasma by LC-MS/MS (Study# 155-1033, sponsor ref# CC-10004-DMPK-041)
70. A final summary report of the in vivo pharmacokinetic and ADME data generated on five Celgene PDE-4 inhibitors in the rat and ferret (Study# GSK 121001)
71. Determination of the oral pharmacokinetics and bioavailability of racemic (b) (4) and its enantiomers in the male and female rat (Study# 1398/215-D1140)

72. Investigation into the pharmacokinetics, excretion and metabolism of [^{14}C]-CC 10004 in the male and female rat following single and repeated oral administrations (Study# 1398/259-D1145)
73. (^{14}C)-CC-10004: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the mouse (Study# 1398/376-D1145)
74. (^{14}C)-CC-10004: A pilot study of plasma pharmacokinetics following oral administration to the rabbit (Study# 1398/387-D1145)
75. (^{14}C)-CC-10004: A study of absorption, excretion and metabolism following oral and intravenous administration to the cynomolgus monkey (Study# 1398/399-D1145)
76. CC-10004: Oral pharmacokinetics and dosing formulation ((b) (4)) evaluation in fasted male rats (Study# CC-10004-DMPK-007)
77. Intravenous and oral (stomach tube) pharmacokinetic study of CC-10004 in pregnant rabbits (Study# CC-10004-DMPK-009)
78. Vehicle tolerance and pharmacokinetic study for CC-10004 in rabbits via oral (stomach tube), intravenous and subcutaneous routes (Study# CC-10004-DMPK-028)
79. In vitro protein binding determination of CC-10004 in mouse, rat, rabbit, monkey, and human plasma using ultrafiltration and LC/MS/MS analysis (Study# CC-10004-DMPK-026)
80. Determination of lacteal transfer of CC-10004 following a single oral dose to lactating CD-1 mice (Study# CC-10004-DMPK-034)
81. Metabolism of (^{14}C)-CC-10004 and (b) (4) in microsomes isolated from mouse, rat, rabbit, dog, monkey, and man (Study# 1398/261-D1145)
82. In vitro metabolism of [^{14}C]-CC-1 0004 in hepatocytes from the mouse, rat, rabbit, dog, monkey, and human (Study# CC-10004-DMPK-023)
83. Metabolite radio-profiling and identification after a single oral and IV dose of (^{14}C)-CC-10004 in male intact and BDC mice (Study# CC-10004-DMPK-031)
84. In vitro metabolism of CC-10004 in adult and juvenile human cryopreserved hepatocytes, human microsomes and CD-1 mouse microsomes (Study# CC-10004-DMPK-038)
85. Elimination of radioactivity in bile, urine, and feces following oral and intravenous administration of (^{14}C)-CC-10004 to mice (Study# CC-10004-DMPK-030)
86. Effects of CC-10004 on selected cytochrome P450 activities in human liver microsomes: prediction of drug interactions (Study# 1398/227-D1145)
87. Identification of the cytochrome P450 enzymes responsible for the in vitro metabolism of (^{14}C)-CC-10004 in human liver microsomes (Study# 1398/393-D1145)
88. In vitro evaluation of CC-10004 as an inducer of cytochrome P450 expression in cultured human hepatocytes (Study# CC-10004-DMPK-012)
89. Assessment of the interaction of CC-10004 with human P-glycoprotein (Study# CC-10004-DMPK-017)
90. Assessment of interaction of CC-10004 with human organic anion transporters using influx transporter cRNA injected xenopus laevis oocytes (Study# 300851854, sponsor ref# CC-10004-DMPK-027)

91. In vitro assessment of inhibition potential of CC-10004 for efflux transporters (Study# CC-10004-DMPK-036)
92. In vitro evaluation of CC-10004 as an inhibitor of human cytochrome P450 enzymes CYP2A6, CYP2B6 and CYP2C8 (Study# CC-10004-DMPK-039)
93. CC-10004: Inhibition potential in OCT2, OATP1B1 and OATP1B3 expressing HEK293 cells (Study# CC-10004-DMPK-040)
94. Evaluation of substrate potential of CC-10004 for uptake (OAT1, OAT3, OCT2, OATP1B1, and OATP1B3) and efflux (BCRP) transporters (Study# XS-0327, sponsor ref# CC-10004-DMPK-1347)

General Toxicology Studies:

95. CC-10004: Single dose oral toxicity study in the rat (Study# 1398/276)
96. CC-10004: Single dose intravenous toxicity study in the rat (Study# 1398/277)
97. CC-10004: Single dose oral toxicity study in the mouse (Study# 1398/278)
98. CC-10004: Single dose intravenous toxicity study in the mouse (Study# 1398/279)
99. CC-10004: 14 day oral (gavage) administration range-finding study in the mouse (Study# 1398-262)
100. CC-10004: 28 day oral (gavage) administration toxicity study in the mouse (Study# 1398-289)
101. CC-10004: 4 week oral (gavage) administration toxicity study in the mouse (Study# 1398-297)
102. CC-10004: 4 week oral (gavage) administration toxicity study in the mouse (Study# 1398-333)
103. CC-10004: 13 week oral (gavage) administration toxicity study in the mouse (Study# 1398-373)
104. CC-10004: A 90-day oral toxicity study in mice (Study # CC-10004-TOX-002)
105. CC-10004: A 6-month oral toxicity study in mice (Study # CC-10004-TOX-004)
106. CC-10004: maximum tolerated dose (MTD) followed by a 14 day fixed dose oral (gavage) administration toxicity study in the monkey (Study# 1398-283)
107. CC-10004: 28 day oral (gavage) administration toxicity study in the monkey (Study# 1398-296)
108. CC-10004: 13 week oral (gavage) administration toxicity study in the monkey (Study# 1398-368)
109. 14-day oral (gavage) pilot study with CC-10004 in cynomolgus monkeys (Study# CC-10004-TOX-010)
110. CC-10004: A 12-month oral toxicity study in cynomolgus monkeys (Study# CC-10004-TOX-005)
111. CC-10004: 90-day oral toxicity study in rats (Study # CC-10004-TOX-003)
112. CC-10004 and (b) (4) Oral (gavage administration) comparative toxicity study in the female rat (Study# 1398/213)
113. CC-1004: Oral toxicity study in mice to investigate the time course for development and recovery of inflammatory lesions in multiple tissues (Study# CC-10004-TOX-008)

Genotoxicity Studies:

114. CC-10004: Reverse mutation in five histidine-requiring strains of Salmonella typhimurium (Study# 1398-282)
115. CC-10004: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes (Study# 1398-280)
116. CC-10004: Induction of micronuclei in the bone marrow of treated mice (Study# 1398-281)
117. Bacterial Reverse Mutation Assay (Study# CC-10004- (b) (4), an impurity)

Carcinogenicity Studies:

118. A 104-week oral carcinogenicity study of CC-10004 in mice (Study# CC-10004-TOX-006)
119. CC-10004: A 104-week oral carcinogenicity study in rats (Study# CC-10004-TOX-007)

Reproductive and Developmental Toxicology Studies:

120. CC-10004: Oral (gavage) fertility and general reproduction toxicity study in mice (Study# CC-10004-TOX-001)
121. Oral (gavage) fertility and general reproduction toxicity study of CC-10004 in male mice (Study# CC-10004-TOX-011)
122. A histopathology expert report for an oral (gavage) fertility and general reproduction toxicity study in mice, a 90-day oral toxicity study in mice, a 6-month oral toxicity study in mice, and an oral (gavage) fertility and general reproduction toxicity study in male mice (sponsor ref# CC-10004-TOX-001, 002, 004, 011)
123. Combined oral (gavage) fertility and developmental toxicity study of CC-10004 in female mice (Study# CC-10004-TOX-012)
124. CC-10004: Oral (gavage) preliminary study in the non-pregnant rabbit (Study# 1398/290)
125. CC-10004: Oral (gavage) range-finding study of embryofetal development in the rabbit (Study# 1398-291-D6145)
126. CC-10004: Oral (gavage) study of embryofetal development in the rabbit (Study# 1398-292)
127. CC-10004: Oral (gavage) range-finding study of embryofetal development in the mouse (Study# 1398-308)
128. CC-10004: Oral (gavage) study of embryofetal development in the mouse (Study# 1398-309)
129. Intravenous dosage-range finding developmental toxicity study of CC-10004 in rabbits (Study# CC-10004-TOX-009)
130. Oral (gavage) embryo-fetal development study with CC-10004 in the cynomolgus monkey (Study# CC-10004-TOX-013)
131. Oral (gavage) developmental and perinatal/postnatal reproduction toxicity study of CC-10004 in mice, including maternal function and postnatal behavioral/functional evaluation (Study# 20012281, sponsor ref# CC-10004-TOX-1139)

132. Two-week oral (gavage) dosage range finding repeated-dose toxicity study of CC-10004 in neonatal mice (Study# CC-10004-TOX-014)

Special Toxicology Studies (including Local Tolerance Studies):

133. Technical memo AP1012R: Evaluation of biomarkers for predicting a pro-inflammatory syndrome caused by CC-10004 in rat
134. An acute dermal irritation study in rabbits of CC-10004 in ethanol:propylene glycol (Study# 847-010, sponsor ref# CC-10004-TOX-500)
135. A skin sensitization study (Buehler method) in guinea pigs of CC-10004 in ethanol:propylene glycol (Study# 847-011, sponsor ref# CC-10004-TOX-501)
136. Neutral red uptake phototoxicity assay of CC-10004 in Balb/c 3T3 mouse fibroblasts (Study# 20020536, sponsor ref# CC-10004-TOX-1170)

3.2 Studies Not Reviewed

Pharmacology studies:

137. Ulcerative colitis biomarker profiling for Phosphodiesterase-4 inhibitors CC-10004, CC-11050 and tetomilast, and cyclosporine A in human peripheral blood mononuclear cells (Study# 5478-100)
138. BioMAP profiling study (Study# BSK-1073)
139. MDS Pharma Services Pharmacology Data Report on Compounds (b) (4) CC-10004 to CG-127, CC-11050 for Celgene Corporation (Study# 1016668)
140. Effect of CC-11050 and CC-10004 in a murine ovalbumin-induced asthma model (Study# AP1217R, AP1356R)
141. Effect of CC-10004 on LPS-induced lung neutrophilia in the rat (Study# AP576, AP600, AP1025)
142. Effect of CC-10004 in a murine ovalbumin-induced asthma model (Study# AP998R, AP1036R)
143. Effects of CC-10004 and CC-11050 on allergen-induced bronchospasm in actively sensitised, anaesthetised, ventilated guinea-pigs (Study# DLXJ1000)
144. CC-10004: changes in disease onset and life span in the G93A SOD1 mouse model of ALS (Study# DRXL-001-CC-10004)
145. The efficacy of CC-10004, CC-11050 and Tetomilast in a TNBS-induced colitis model (Study# EpiStem 06-218c)
146. The efficacy of CC-10004, CC-11050 and tetomilast in a TNBS-induced colitis model: further gene expression analysis (Study# EpiStem 07-163)
147. Analgesic assessment of test articles in the Bennett (CCI) model of neuropathic pain (Study# S07059)
148. The Effect of PDE4 Inhibitors and IMiDs on GMCSF production by normal human lung fibroblasts (Study# 5369-006-041)

Note:
Most studies have been reviewed under IND 70270. A number of pivotal studies, including two carcinogenicity studies and a peri- and post-natal development study in mice, were reviewed under NDA 205437. Some pharmacology studies were not

reviewed because they were either not relevant to the indication (psoriasis) or did not provide additional useful information for safety assessment. Nonclinical information from previous reviews and from the approved label for OTEZLA under NDA 205437 is summarized/cited in this review.

3.3 Previous Reviews Referenced

- Nonclinical reviews, IND 70270, by Dr. Paul Brown, dated 09/07/2005 and 12/02/2005
- Nonclinical reviews, IND 70270, by Dr. Barbara Hill, dated 09/28/2006, 11/02/2006, 06/19/2007, 09/25/2007, 12/10/2007, 04/30/2008, 07/21/2009, and 04/04/2012
- Nonclinical reviews, IND 70270, by Dr. Carmen Booker, dated 08/26/2010, 11/24/2010, and 05/13/2011
- Nonclinical review, IND 101761, by Dr. L. Steven Leshin, dated 12/06/2010
- Nonclinical review, NDA 205437, by Dr. L. Steven Leshin, dated 11/20/2013

4 Pharmacology

4.1 Primary Pharmacology

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. From published literature, it is known that the inhibition of PDE4 results in increased levels of intracellular cAMP, initiation of an intracellular signaling pathway that involves the activation of protein kinase A, and activation of cAMP responsive element binding protein (CREB) family of transcription factors, as well as down-regulation of nuclear factor kappaB (NF-κB) transcriptional activity. It has been demonstrated that CC-10004 alters many pro- and anti-inflammatory mediators in numerous in vitro and/or in vivo conditions, including TNF-α, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IL-23, (b) (4) and IFN-γ. The sponsor proposed that the ability of CC-10004 to modulate levels of pro- and anti-inflammatory mediators will provide therapeutic benefits in psoriasis patients.

In vitro

CC-10004 had an IC_{50} of 74 nM for PDE4 isolated from U937 human monocytic cells (b) (4). CC-10004 was approximately 279- to 40,000-fold more selective for PDE4 inhibition than for other PDE subtypes, but was non-selective for subtypes A1A, B1, B2, C1, and D2 within the PDE4 group.

CC-10004 inhibits LPS-induced TNF-α and IL-12 release from PBMC and increases IL-10 release in the same test system. TNF-α release from PBMC induced by IL-1 β was also reduced by CC-10004. Staphylococcal enterotoxin B induced IL-2 and IFN-γ production from PBMC was inhibited by CC-10004. IL-5 production from stimulated $CD4^+$ T cells was inhibited by CC-10004. CC-10004 inhibited IL-1β stimulated (b) (4) production in human endothelial cells. CC-10004 was shown to cause a dose-

dependent elevation of IL-6 production from LPS-stimulated whole blood from the mouse and rat but not from monkey or human in vitro. CC-10004 inhibited TNF-α, IL-12/IL-23 p40, IL-23 p19, total IL-23, IFN-γ inducible protein 10 (IP-10), and MCP-1 production in LPS-stimulated human whole blood. CC-10004 inhibited fMLF-induced neutrophil LTB4 production and fMLF-induced neutrophil adhesion to endothelial cells. CC-10004 inhibited VEGF-induced proliferation of human umbilical vein endothelial cells in a concentration-dependent manner.

In vivo

In the BALB/c mouse LPS-induced serum TNF-α model, apremilast (0.01 - 1 mg/kg, PO) demonstrated potent inhibition of TNF-α increase. Similarly, in the rat LPS-induced TNF-α release model, apremilast (0.1 - 10 mg/kg, PO) also reduced LPS-induced plasma TNF-α level. Apremilast was also tested in the rat carrageenan-induced inflammation/hyperalgesia model. Apremilast (50 mg/kg, IP) significantly reduced rat paw edema; while in a similar study, an oral dose of apremilast (10 mg/kg) had no effect on paw edema following carrageenan injection.

Apremilast was evaluated and compared to cyclosporine in a human NK cell driven model of psoriasis that utilized human skin xenotransplanted onto severe combined immunodeficiency (SCID) mice. Results showed that both apremilast and cyclosporine (each at 5 mg/kg/day, 2.5 mg/kg/day BID) caused statistically significant reductions in both epidermal thickness and keratinocyte proliferation index as compared to the vehicle control. In addition, both test articles caused reductions in the psoriasisform histological features and immunohistochemical expression of the inflammatory markers TNF-α, HLA-DR and ICAM-1.

In an UVB-stimulated cell apoptosis model, apremilast can inhibit apoptotic cell death within the epidermis of SKH-1 hairless female mice when administered orally at 25 mg/kg 1 hour before UVB exposure.

4.2 Secondary Pharmacology

Refer to Section 4.1.

4.3 Safety Pharmacology

CNS effects:

The general behavioral effects of single oral dose administration of CC-10004 [0 (vehicle: 1% carboxymethylcellulose), 500, 1000, and 2000 mg/kg] were evaluated in male CD-1 mice. The NOAEL for general behavioral effects after a single oral dose in male mice was 500 mg/kg. Higher doses produced relatively minor effects including lacrimation, ptosis and apathy.

Cardiovascular and pulmonary effects:

CC-10004 inhibited the hERG channel current only partially and only at very high concentrations (IC_{50} = 184.2 μM). The mean maximum inhibition produced by CC-10004 was 59.0% and occurred at the high dose of 249.7 μM. By comparison the positive control, terfenadine, produced a mean inhibition of 87.1% at 60 nM. CC-10004 appears to be a very low potency inhibitor of the hERG channel.

The cardiovascular and pulmonary effects of single IV dose administration of CC-10004 [0 (vehicle: 8% DMSO in intralipid), 0.5, 1 and 5 mg/kg] was evaluated in anesthetized Beagle dogs. CC-10004 induced a dose-related increase in dP/dt_{max} and heart rate in dogs. Corrected QT interval was not affected in this study. Peak inspiratory flow and peak expiratory flow were both increased with increasing dose in this study. The results suggest that CC-10004 does not have a high risk for producing QT prolongation.

Intestinal mobility:

Oral (gavage) administration of CC-10004 at doses up to 1000 mg/kg to male mice had no effect on intestinal mobility (distance traveled of an oral gavage administered charcoal suspension).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

PK studies were conducted in mice, rats, rabbits, and monkeys. Liquid chromatographic analytical methods with tandem mass spectrometric detection (LC-MS/MS) were developed and validated for the measurement of apremilast (S enantiomer), [redacted] (b) (4) and its metabolites in PK/TK studies.

Absorption

In CD-1 mice, when [^{14}C]-CC-10004 was administered intravenously at 10 mg/kg or orally at 500 mg/kg, oral bioavailability ranged from approximately 20% to 33% (average 27%). With oral dosing, the terminal elimination half-life of [^{14}C]-CC-10004 was approximately 15 hr in males and 22 hr in females. In cynomolgus monkeys, the bioavailability of total administered radioactivity was approximately 78% for a 10 mg/kg oral dose. In SD rats, males metabolized CC-10004 more extensively than females. There was greater systemic exposure to CC-10004 in female rats than male rats, following either oral administration (10 or 50 mg/kg, 32-85-fold greater in females) or IV administration (5 mg/kg dose, 4-6-fold greater in females). The bioavailability following oral dosing of CC-10004 was approximately 12% in males and 63% in females. In rabbits, the exposure to CC-10004 following oral dosing was minimal (bioavailability < 1%). The metabolism of CC-10004 by rabbit microsomes under in vitro conditions occurred faster than other species examined. Other factors such as instability in frozen samples might also have contributed to the measured poor bioavailability in rabbits. Cynomolgus monkey was therefore used as an alternative species for embryofetal developmental toxicology studies.

Distribution

Quantitative whole body radiography was conducted in mice. After oral administration the highest levels of radioactivity were detected in the gastrointestinal tract, kidney, liver and pancreas. The CNS tissues appeared to have lower levels than most other tissues. Skin levels were similar to other tissues and decreased with time. By 72 hr only the liver had quantifiable levels of radioactivity and by 168 hr no radioactivity was detected in any tissue in albino mice.

Plasma protein binding of CC-10004 was measured in mouse, rat, rabbit, monkey and human plasma. The overall mean CC-10004 percent bound was 88.6% in mouse plasma, 90.6% in rat plasma, 80.9% in rabbit plasma, 84.3% in monkey plasma and 68.3% in human plasma at the tested concentration range of 0.25 - 2.5 µg/ml. The results indicate that significantly less plasma protein binding of CC-10004 occurs in humans compared to other tested species.

Lactating CD-1 mice (at ~Day 13 of lactation) were administered a single oral dose of 10 mg/kg CC-10004 in 1% carboxymethylcellulose vehicle. Milk and plasma was collected at 1, 6, and 24 hr postdose. The peak average concentrations of CC-10004 occurred at 1 hr postdose, and were 984 and 1441 ng/ml in plasma and milk, respectively. Concentrations were below the limit of quantitation (3 ng/ml) by 24 hr postdose. The average milk to plasma concentration ratios were 1.46 and 1.62 at 1 and 6 hr postdose.

Placental transfer was examined in the mouse and monkey embryofetal developmental studies. In both species, CC-10004 was detected in the fetal compartments.

Metabolism

Major metabolites of CC-1004 are shown in the following table. There were no unique metabolites identified in humans that were not identified in animal species used in toxicology studies (mouse, rat and monkey).

Transformation (Celgene compound number)	MW daltons	Human (Report CC-10004-PK-002)	Mouse (Report CC-10004-DMPK-031)	Mouse (Report 1398/376-D1145)	Rat (Report 1398/259-D1145)	Monkey (Report 1398/399-D1145)
Apremilast (CC-10004)	460	Parent	Parent	MuU22, MuF22, MuP22	RP20, RU20, RF20	MkP24, MkF24
Hydrolysis products (CC-15091)	478	M1/M2		MuP10/P11, MuU11[a], MuF10/F11	RP10/P11, RU10/U11, RF10/F11	MkP13, MkP14, MkU11
O-Demethylated (CC-16085)	446	M3	M3	MuF20	RP18, RU18, RF18	MkU22, MkF22
O-Demethylated *N*-deacetylated	404	M4				MkF21
O-Deethylated (CC-10047)	432	M5[b]	M5	MuU17	RP16, RU16, RF16	
N-Deacetylated (CC-10055)	418	M7	M7		RP14, RF14	
Hydroxylated *O*-demethylated *N*-Deacetylated	420	M8			RF15	
Hydrolysis products of M3	464	M9		MuF8, MuF9	RP7/P8, RU7/U8, RF7/F8	MkU9/U10, MkF9/F10
O-Demethylated hydroxylated acetamide	462	M10				MkF20
Hydroxylated *N*-deactylated	434	M11	M11			
O-Demethylated glucuronide (CC-16166)	622	M12	M12	MuU12	RP12, RU12, RF12	MkP15, MkU14
O-Deethylated glucuronide	608	M13	M13	MuU11[a]		MkU13[a]
N-Deacetylated M12	580	M14	M14			
Hydrolysis products of M12	640	M15	M15	MuP3, MuU2		MkP6, MkP7, MkU4, MkU5
Hydroxylated acetamide glucuronide (CC-16557)	652	M16	M16			
Hydroxylated acetamide (CC-16401)	476	M17	M17			
3-Acetamide-phthalic acid	223	M18	M18			
O-Demethylated *O*-deethylated	418	M19	M19	MuF14		MkF16
N-Deacetylated *O*-demethylated *O*-deethylated	376	M20	M20			
O-Demethylated *O*-deethylated hydroxylated acetamide	434	M21	M21			
Hydrolysis products of M5	450	M22		MuF6, MuF7		
Hydrolysis product of hydroxylated acetamide	239	M23	M23			

MW = molecular weight.

[a] MuU11 and MkU13 peaks contained hydrolysis product of apremilast and *O*-Deethylated glucuronide

[b] M5 was not detected in humans

In vitro

In liver microsome metabolism, the order of the extent of metabolism from high to low was rabbit >> monkey > mouse = male rat > human > dog > female rat. The rat was the only species with sex differences in the metabolism of CC-10004.

In hepatocyte metabolism, [^{14}C]-CC-10004 was metabolized most extensively by rabbit hepatocytes, moderately by rat hepatocytes, and to a limited extent by hepatocytes from the mouse, dog, monkey, and human. Twelve metabolites (M1/M2, M3, M4, M7, M11, M12, M14, M15, M16, M17, M18 and M23) were characterized or identified. All metabolites formed in vitro by human hepatocytes were formed by hepatocytes from one or more animal species, although the amounts differed among the species.

In human liver microsomes, [^{14}C]-CC-10004 was mainly metabolized to four products, designated as M1, M2, M3, and M5. (b) (4)

Metabolites M3 and M5 were not produced to an appreciable extent in the absence of NADPH, indicative of the involvement of CYP enzymes. CYP3A4 was subsequently confirmed to be the major CYP enzyme in metabolizing CC-10004 to M3 and M5.

CC-10004 did not significantly inhibit marker enzyme activities for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. CC-10004 was a weak direct inhibitor of CYP2C8 (estimated IC_{50} = 56.1 µM).

Treatment of cultured human hepatocytes with CC-10004 (1, 10, and 100 µM) had little or no effect on CYP2B6 and CYP2C19. It had no effects on CYP1A2 and CYP2C9 at 1 µM; while a decrease in CYP1A2 and CYP2C9 activities were noted at higher concentrations (35% at 10 µM, up to 70% at 100 µM). There was no effect on CYP3A4 activities at 1 or 10 µM. A 3.7-fold induction of CYP3A4 (roughly half the extent induced by rifampin) was observed at 100 µM. However, this effect is unlikely to be clinically relevant because 100 µM is approximately 70-fold higher than the observed C_{max} of apremilast in psoriasis patients following 30 mg BID dosing (approximately 1.5 µM).

In vivo

Mouse
A single dose of [^{14}C]-CC-10004 was administered either orally by gavage (500 mg/kg) or intravenously (10 mg/kg) to mice. The metabolite profiles obtained from plasma, urine, and feces were qualitatively similar for both routes and both sexes. Hydrolysis products M1 and M2 were the major components of plasma radioactivity. Metabolites detected in urine and feces included M1/M2, M3, M9, M12, M15, M19 and M22. In another PK study in mice, after a single oral dose of 10 mg/kg, or a single IV dose of 5 or 10 mg/kg [^{14}C]-CC-10004, unchanged CC-10004 and M12 were the major components in mouse plasma.

Rat
[^{14}C]-CC-10004 was administered orally, either as a single dose at 10 mg/kg or as a single dose preceded by 6 daily doses of non-radiolabeled CC-10004 (10 mg/kg/day), in

order to assess the effect of repeated dosing. Unchanged CC-10004 was minimal in male rat plasma. The major metabolites in male plasma were an unidentified, early eluting component (RP1) and M12; whereas in females unchanged CC-10004, RP1, M1/M2, and M12 were detected. The amounts of [^{14}C]-CC-10004 parent and M1/M2 were greater in females than males.

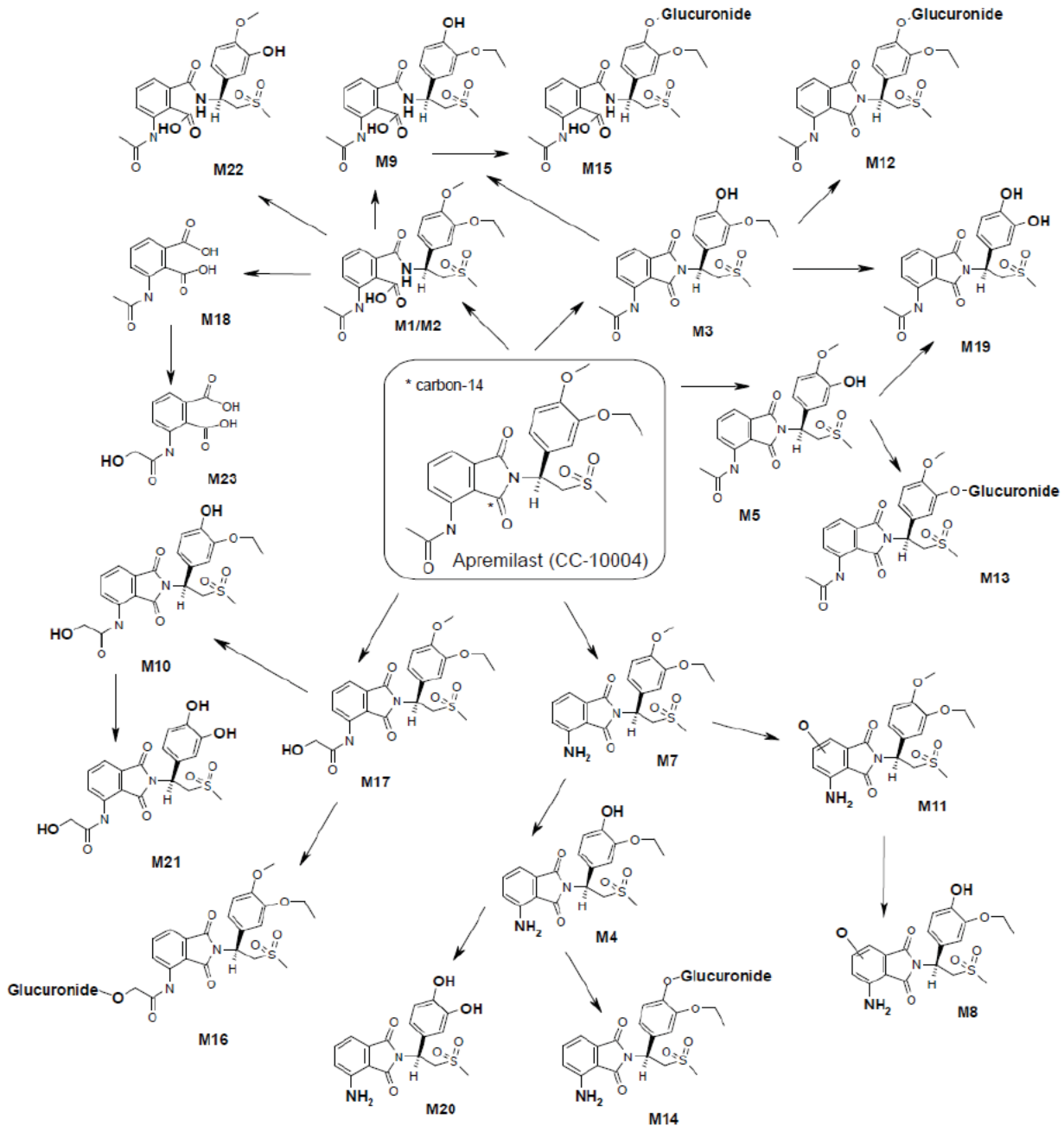
Rabbit
The rabbit had negligible CC-10004 exposure in the embryofetal development toxicology studies (Reports 1398/290, 1398/291, and 1398/292) and an alternative species (monkey) was selected for study. One animal contained a glucuronic acid conjugate of O-desmethyl-CC-10004 (M12), which was interpreted to probably be a major metabolite.

Monkey
Cynomolgus monkeys were administered [^{14}C]-CC-10004, an IV dose of 1 mg/kg and an oral dose of 10 mg/kg in a crossover design with a 28-day period between treatments. The metabolites observed in plasma include M1, M2, and M12, in addition to two polar metabolites (MkP2 and MkP3), which could not be identified due to interference from high levels of endogenous material. Two minor metabolites were identified as the two isomers of M15 (O-desmethyl hydrolyzed apremilast glucuronide). Little or no [^{14}C]-CC-10004 parent was excreted in urine or feces.

The following comments were cited from Dr. Leshin's review for NDA 205437:

"In the clinical study of CC-10004-PK-002, the major metabolite was M12, (CC-16166, O-demethylated glucuronide), comprising about 86% of the total radioactive dose of [^{14}C]-CC-10004. Although the levels of this metabolite were much greater than in the toxicological study species, M12 was a glucuronide conjugate and it was not necessary to conduct further toxicological assessments, since glucuronides are pharmacologically and probably toxicologically inactive."

The proposed metabolic pathways of apremilast are shown below:



Ring-hydrolyzed metabolites M1 and M2 are represented as one structure.

Figure 1. The proposed metabolic pathways of apremilast.

Elimination

Biliary excretion with fecal elimination is the major route of CC-10004 excretion in the mouse and monkey. This was demonstrated in studies comparing samples from intact and bile duct cannulated mice. Although there were no bile duct cannulated monkeys,

intravenous administration of [^{14}C]-CC-10004 resulted in high amounts of radioactive fecal elimination which is explained by biliary excretion.

CC-10004 is extensively metabolized. Except for the mouse, there is less unchanged CC-10004 excreted in the animal studies than for humans. The major excreted form in humans is M12 the O-demethylated glucouronide (34%) and M3 the O-demethylated product (5-8%), with 7% unchanged CC-10004. In the monkey, M9 the hydrolysis products of O-demthylation (28-40%), and M3 (9-17%) are the major excretion forms, with very little up to 0.05% unchanged CC-10004. In the mouse, M12 (37% in one study), M13 the O-deethylated glucuronide (13%), M9 (13-14%), and M3 (6-8%) were the major excretion forms, with unchanged CC-10004 comprising 4% or 16-23% depending on the study.

5.2 Toxicokinetics

Included in toxicology studies.

6 General Toxicology

6.1 Single-Dose Toxicity

Single IV and oral dose toxicity studies were conducted in mice and rats. The minimum lethal dose of CC-10004 after single IV administration appears to be (b) (4) mg/kg in mice and between (b) (4) mg/kg in rats. The minimum lethal dose of CC-10004 in mice after single oral administration appears to be greater than (b) (4) mg/kg. A sex difference was apparent in rats after single oral dose administration. The minimum lethal dose of CC-10004 appears to be (b) (4) mg/kg or greater in males and (b) (4) mg/kg in females.

Due to pronounced sex differences in PK and toxicity profiles of CC-10004 in rats, mouse and monkey were used in subsequent pivotal repeat-dose toxicology studies. A 2-year oral carcinogenicity study and its dose range-finding study were conducted in rats.

6.2 Repeat-Dose Toxicity

1. CC-10004: 4-week oral toxicity studies in mice

Three 4-week oral mouse toxicity studies were conducted with CC-10004. Oral (gavage) doses of 0 (1% carboxymethylcellulose), 250, 600 and 1500 mg/kg/day CC-10004 were administered in the first study. Oral (gavage) doses of 0 (same vehicle), 5, 25, 75 and 150 mg/kg/day CC-10004 were administered in the second study. Oral (gavage) doses of 0 (same vehicle), 1, 2, and 4 mg/kg/day CC-10004 were administered in the third study. Arteritis was a major toxicity findings noted in these studies. It occurred in a variety of tissues and appeared to be associated with a general inflammatory reaction. The arteritis was described as acute inflammatory cell infiltrate

in all layers of the vessel wall, perivascular edema and hemorrhage, disruption of the elastic lamina, occasional minor areas of necrosis and areas of fibrosis.

Arteritis was noted at doses as low as 5 mg/kg/day. The NOEL was 4 mg/kg/day for both males and females. Other findings included neutrophil and globulin level increase, centrilobular liver hypertrophy, hyperkeratosis and gastritis of the stomach, hemopoiesis in the spleen, and lymphoid hyperplasia in lymph nodes and thymus. Day 28 AUC_{0-24} values are shown in the table below:

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
1	841.8	881.8
2	2176.1	1375.5
4	3809.7	3991.9

2. CC-10004: 13-week oral toxicity studies in mice

Oral (gavage) doses of 0 (1% carboxymethylcellulose), 2, 4, 8 and 16 mg/kg/day CC-10004 (micronized, diameter = (b) (4)) were administered to CD-1 mice for 13 weeks. Arteritis in the root of the aorta and the thymus and minor perivascular inflammatory cell infiltration in the lung were noted at 16 mg/kg/day. No arteritis or other toxicities were observed at 8 mg/kg/day or lower. The NOAEL was identified as 8 mg/kg/day. TK parameters are shown in the table below.

Dose (mg/kg/day)	$AUC_{0-24\ hr}$ (ng·hr/ml)		C_{max} (ng/ml)	
	Males	Females	Males	Females
Day 1				
2	2315	2607	443	508
4	4743	4993	982	757
6	10721	7865	1305	1348
8	13736	17414	2531	2310
Week 13				
2	2143	2418	351	508
4	4069	4764	613	748
6	9608	8988	991	1003
8	15960	14895	1782	1725

A second 13-week toxicity study was conducted with CC-10004 (milled; diameter = 64.2 microns). Oral (gavage) doses of 0 (same vehicle), 100, 300 and 1000 mg/kg/day CC-10004 were administered to mice for 13 weeks. No treatment-related mortality was noted in this study. A treatment-related inflammation manifested by a neutrophilic leukocytosis, lymphopenia and increased acute phase proteins (haptoglobin and CRP) was noted in low, mid and high dose animals during Week 1 but not in Week 13. Treatment-related histopathological findings included inflammatory lesions noted in the lung, heart and aortic root in mid and high dose animals. The NOAEL for this study could be identified as 100 mg/kg/day CC-10004, since the inflammatory effects induced by CC-10004 were transient. TK parameters are shown in the following table.

Dose (mg/kg/day)	$AUC_{0-24\ hr}$ (ng·hr/ml)		C_{max} (ng/ml)	
	Males	Females	Males	Females
Day 1				
100	27604	36367	4981	3865
300	58967	87410	5542	8436
1000	101553	158833	8027	17213
Day 27				
100	25483	20135	3388	2853
300	72764	60045	4882	4184
1000	82270	93969	6457	6441
Day 86				
100	24318	25417	2925	2967
300	52419	54890	4078	4318
1000	80724	87828	5196	6442

The results from human comparative PK study indicated that there was a modest increase in systemic exposure to CC-10004 in the subjects administered micronized drug compared to milled drug; however, the difference in exposure is substantially less in humans compared to what was noted in mice.

3. CC-10004: a 6-month oral toxicity study in mice

Oral (gavage) doses of 0 (1% carboxymethylcellulose), 10, 100 and 1000 mg/kg/day CC-10004 (milled) were administered to CD-1 mice for 6 months. Treatment related mortality was noted in mid and high dose groups. Treatment-related histopathological findings noted in mid and high dose animals included: lesions in the heart that involved inflammation of the aortic root or around the cardiac arteries and in the myocardium, cartilaginous metaplasia of the aortic root along with vascular mineralization, vascular inflammation, hematoma formation and centrilobular hepatocellular hypertrophy of the liver. Additional lesions included vascular inflammation and hematoma in the mesentery adjacent to the pancreas of one high dose female and necrosis, fibroplasia and inflammation in the gallbladder of another high dose female. Vascular and perivascular inflammation of the liver and fibrosis around the bile ducts was noted in one mid dose male. The NOAEL was identified as 10 mg/kg/day. Day 177 AUC_{0-24} values of CC-10004 at 10 mg/kg/day were 5614 and 5842 ng•hr/ml, in males and females, respectively.

4. CC-10004: a 13-week oral toxicity study in rats

This study was conducted with CC-10004 (milled; diameter = (b) (4)) as a dose range-finding study for a 2-year carcinogenicity study. Oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 0.3, 3, 10 and 30 mg/kg/day were administered to female SD rats for 90 days while oral (gavage) doses of 0 (vehicle), 30, 100, 300 and 1000 mg/kg/day were administered to male SD rats for 90 days. Due to mortality dosing was discontinued in the following dose groups: 1) mid-low dose males on Day 48, 2) mid-high dose males on Day 11, 3) mid-high dose females on Day 26, and 4) high dose animals on Day 9. CC-10004 caused acute inflammation and lymphoid depletion in multiple tissues in all dose groups manifested clinically by prostration and a

neutrophilic leukocytosis, increased acute phase proteins (haptoglobin) and decreased albumin. Lethality was noted in all male dose groups and the mid-high and high dose females. A NOAEL could not be identified in this study based on the microscopic findings of lymphoid depletion and/or subacute inflammation of the thymus, small intestines and/or mesentery noted in all dose groups. The MTD of CC-10004 after administration to rats for 90 days is identified as 30 mg/kg/day in male rats and 3 mg/kg/day in female rats.

5. CC-10004: a 4-week oral toxicity study in monkeys

Oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 50, 180 and 650 mg/kg/day CC-10004 (micronized) were administered to cynomolgus monkeys for 4 weeks. Increased neutrophil levels and slight increases in liver weight were noted in all drug treated groups. Several occurrences of vasculitis were noted in the mid and high dose groups although these were infrequent and did not follow a dose response. A NOEL was not identified, although the 50 mg/kg dose might be a NOAEL if the increased neutrophils and slight liver weight increases are not considered adverse. Day 28 AUC_{0-24} values are shown in the table below.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
50	15079.0	9665.6
180	52892.7	34772.4
650	78988.8	58271.1

6. CC-10004: a 13-week oral toxicity study in monkeys

Oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 25, 85 and 300 mg/kg/day CC-10004 (micronized) were administered to cynomolgus monkeys for 13 weeks. Possible treatment related effects included salivation in low, mid and high dose groups and vomiting in the high dose group. No vasculitis was noted in this study. Inflammatory cell foci in the liver and throughout the body may have also been slightly elevated in drug treated animals. The NOAEL was identified as 300 mg/kg/day. Week 13 AUC_{0-24} values are shown in the following table.

Dose (mg/kg)	AUC_{0-24} (ng·h/mL)	
	Male	Female
25	13254.2	12460.9
85	12592.2	20293.1
300	32523.2	23306.7

7. CC-10004: a 12-month oral toxicity study in monkeys

Oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 60, 180, and 600 mg/kg/day CC-10004 (milled) were administered to cynomolgus monkeys for 12 months. No treatment-related effects on mortality, body weight, ophthalmic parameters,

ECG parameters, urinalysis parameters, organ weights, macroscopic parameters, or microscopic parameters were noted in this study. Minor hematology and serum chemistry findings noted in mid and high dose groups were not considered significantly adverse due to the absence of any corresponding histopathological findings. The NOAEL was identified as 600 mg/kg/day. Day 358 AUC_{0-24} values of CC-10004 at 600 mg/kg/day were 42608 and 26936 ng•hr/ml in males and females respectively. It would have been preferable if the sponsor had used a higher dose that could induce overt toxicity.

7 Genetic Toxicology

The following genetic toxicology information is contained in the approved OTEZLA label under NDA 205437.

"Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay."

8 Carcinogenicity

The following carcinogenicity information is contained in the approved OTEZLA label under NDA 205437.

"Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors was observed in mice at oral doses up to 8.8 the MRHD on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively)."

9 Reproductive and Developmental Toxicology

The Pregnancy Section in the approved OTEZLA label under NDA 205437 is a hybrid of the current CFR labeling and the expected to-be-established new pregnancy labeling rule. The reproductive and developmental toxicology information contained in the approved OTEZLA label is as follows:

"*Pregnancy Category C:*

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972.

Risk Summary
Adequate and well-controlled studies with OTEZLA have not been conducted in pregnant women. In animal embryo-fetal development studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related

increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximal recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. In mice, there were no apremilast induced malformations up to exposures 4.0-times the MRHD. The incidences of malformations and pregnancy loss in human pregnancies have not been established for OTEZLA. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Labor or delivery
The effects of OTEZLA on labor and delivery in pregnant women are unknown. In mice, dystocia was noted at doses corresponding to ≥ 4.0-times the MRHD (on an AUC basis at doses ≥ 80 mg/kg/day) of apremilast.

Animal Data
Monkey embryo-fetal development: In an embryo-fetal developmental study, cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during weeks 3 to 4 of dosing in the first trimester, at doses approximately 2.1-times the MRHD and greater (on an AUC basis at dose ≥ 50 mg/kg/day). No abortifacient effects were observed at a dose approximately1.4-times the MRHD (on an AUC basis at a dose of 20 mg/kg/day). Although, there was no evidence for a teratogenic effect at doses of 20 mg/kg/day and greater when examined at day 100, aborted fetuses were not examined.

Mouse embryo-fetal development: In an embryo-fetal development study, apremilast was administered at dosages of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation day 6 through 15). In a combined fertility and embryo-fetal development study, apremilast was administered at dosages of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of 2.3-times the MRHD and greater (≥ 20 mg/kg/day). At doses of ≥ 20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately 1.3-times the MRHD (10 mg/kg/day).

Mouse pre- and postnatal development: In a pre- and postnatal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from day 6 of gestation through day 20 of lactation, with weaning on day 21. Dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to ≥ 4.0-times the MRHD (on an AUC basis at dose ≥ 80 mg/kg/day). No adverse effects occurred at a dose 1.3-times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune

competence, or fertility in the offspring at doses up to 7.5-times the MRHD (on an AUC basis at a dose of 300 mg/kg/day).

“It is not known whether OTEZLA or its metabolites are present in human milk; however apremilast was detected in milk of lactating mice. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman.”

“In a fertility study of male mice, apremilast at oral dosages up to approximately 3-times the MRHD based AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral dosages of 10, 20, 40, or 80 mg/kg/day. At dosages > 1.8-times the MRHD (> 20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at dosages of 20 mg/kg/day and greater also had increased incidences of early postimplantation losses. There was no effect of apremilast approximately 1.0-times the MRHD (10 mg/kg/day).”

Reviewer’s comments:
According to Dr. Chinmay Shukla, the clinical pharmacology reviewer for this NDA, the systemic exposure to apremilast (AUC value) is fairly similar among subjects with psoriatic arthritis, rheumatoid arthritis, or psoriasis at MRHD (30 mg BID). Therefore, it is acceptable to use the same multiples of human exposure that were presented in the OTEZLA label approved under NDA 205437 in the drug label for this NDA.

10 Special Toxicology Studies

1. Evaluation of biomarkers for predicting a pro-inflammatory syndrome caused by CC-10004 in rat

A special study of CC-10004 was conducted in rats to assess possible biomarkers of inflammation and vasculitis. The animals were treated by oral gavage with 0 (vehicle: 0.5% carboxymethylcellulose/0.25% Tween-80), 6 or 10 mg/kg/day for 7 days. Some animals were maintained for an additional 11-day recovery period and sacrificed on Day 18 while other animals were sacrificed on Days 3, 6, 8 and 14. CC-10004 caused an acute inflammatory reaction in female rats. This was characterized by an increase in neutrophils (neutrophilic leukocytosis). A variety of biomarkers where shown to be altered. TNF-α, IL-6, G-CSF, CRP, fibrinogen, MCSF, and VEGF all showed increases during treatment. Peritoneal fluid increased (ascites) and analysis of this fluid also showed markers of inflammation. Decreased leptin and increased serum lipase levels suggested that adipocytes may be affected.

2. An acute dermal irritation study in rabbits of CC-10004 in ethanol:propylene glycol

Three female rabbits were each treated with CC-10004 (formulated in the vehicle: ethanol:propylene glycol 40:60% v/v) applied dermally at a dose volume of 0.5 ml (0.3

mg/ml) for 4 hr. The test article was applied to a gauze patch prior to being applied to the animal. The gauze patch was wrapped with semi-occlusive tape. The site was scored using the Draize scale at 30, 60 min, and 24, 48 hr. There was no effect on survival or body weight. There was no dermal irritation in any of the three rabbits. CC-10004 is a not a dermal irritant under the study conditions.

3. A skin sensitization study (Buehler method) in guinea pigs of CC-10004 in ethanol:propylene glycol

In a preliminary dose range-finding study, guinea pigs were treated with CC-10004 (formulated in the vehicle: ethanol:propylene glycol 40:60% v/v) at topical doses of 0, 0.05, 0.5, and 3.0 mg/ml with a dose volume of 0.4 ml. The sites were scored using the Draize scale at 24 and 48 hr. No signs of irritation were noted at any dose. The high dose, 3.0 mg/ml, was therefore used in the sensitization study.

In the skin sensitization study, in induction phase guinea pigs were treated with 3.0 mg/ml CC-10004 or control articles (0.4 ml) applied by a topical patch for 6 hr. The dose was administered to the same site once a week for 3 weeks. The induction phase was followed by a challenge phase and then a rechallenge phase. The challenge applications (0.4 ml) were made to the shaved left (challenge) or right (rechallenge) posterior flank. The sites were scored using the Draize scale at 24 and 48 hr. A severity index (SI = sum of the grades at interval/total number of animals) and a sensitization index (SII = number of animals showing a positive response at 24 and 48 hr/total number of animals x 100%) were calculated. No signs of irritation were noted in the challenge phase in CC-10004 treated animals. However, the positive control group responded in an equivocal manner. Subsequently the test article and positive control groups were rechallenged. In the rechallenge phase, the positive control group responded in a normal manner, while positive signs of irritation were observed in 1 of 20 guinea pigs treated with CC-10004. This resulted in an SII of 5% (Weak Sensitizer).

Under the study conditions, CC-10004 in ethanol:propylene glycol at 3 mg/ml is classified as a weak skin sensitizer.

4. Neutral red uptake phototoxicity assay of CC-10004 in Balb/c 3T3 mouse fibroblasts

The phototoxicity potential of CC-10004 was evaluated in this assay by measuring the relative reduction in viability of Balb/c 3T3 mouse fibroblasts exposed to CC-10004 and UV radiation. Solubility evaluation revealed a solubility limit of 101.8 mg/l CC-10004 in 1 % DMSO/Dulbecco's PBS (DPBS). For UV radiation the cells were exposed to 5 J/cm^2 of UVA and 17 - 25 mJ/cm^2 of UVB (based on historical data) from a xenon arc solar simulator equipped with a Schott WG 320 filter. CC-10004, up to 101.8 mg/l, the maximum feasible concentration in 1% DMSO/DPBS demonstrated no cytotoxic effect (absence of UVR exposure) or phototoxic effect (with UVR exposure) in this assay.

CC-10004 was not phototoxic under the study conditions.

11 Integrated Summary and Safety Evaluation

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. It has been recently approved for the treatment of psoriatic arthritis under NDA 205437. PDE4 inhibition results in increased intracellular cAMP levels, affecting numerous cellular functions in PDE4 responsive cells. It has been demonstrated that CC-10004 alters many pro- and anti-inflammatory mediators in in vitro and/or in vivo conditions, including TNF-α, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17, IL-23, (b) (4) and IFN-γ. Apremilast showed certain efficacy in a human NK cell driven model of psoriasis that utilized human skin xenotransplanted onto SCID mice. The sponsor proposed that the ability of CC-10004 to modulate levels of pro- and anti-inflammatory mediators will provide therapeutic benefits in psoriasis patients.

In safety pharmacology studies, no CNS effects were noted in mice at a single oral dose of 500 mg/kg CC-10004. Minor neurological effects including lacrimation, ptosis and apathy were seen at higher doses. CC-10004 inhibited the hERG channel current only partially and only at very high concentrations (IC_{50} = 184.2 μM). CC-10004 induced a dose related increase in dP/dt_{max} and heart rate in anaesthetized dogs. Corrected QT interval was not affected in this study. Peak inspiratory flow and peak expiratory flow were both increased with increasing dose in this study. The results suggest that CC-10004 does not have a high risk for producing QT prolongation. CC-10004 at single oral doses up to 1000 mg/kg had no effect on intestinal mobility in mice.

PK studies were conducted in mice, rats, rabbits, and monkeys. Oral bioavailability of CC-10004 was ~20-33% in mice, ~78% in monkeys, ~12% in male rats and ~63% in female rats, and < 1% in rabbits. Due to pronounced sex differences in PK and toxicity profiles of CC-10004, rat was not used in pivotal repeat dose toxicology studies. Due to the poor oral bioavailability of CC-10004 in rabbits, monkey was used as an alternative species in reproductive and developmental toxicology studies. The metabolism profile of CC-10004 was generally comparable in humans and animal species used in toxicology studies. There were no unique metabolites identified in humans that were not identified in animal species used in toxicology studies. Although the levels of a major metabolite in humans (M12, O-demethylated glucuronide), were much greater than in the toxicology study species, M12 was a glucuronide conjugate and it was not considered necessary to conduct further toxicological assessments, since glucuronides are generally pharmacologically inactive.

Pivotal repeat dose toxicology studies were conducted in mice and monkeys. Three 4-week oral toxicity studies were conducted in mice. Oral (gavage) doses of 0 (1% carboxymethylcellulose), 250, 600 and 1500 mg/kg/day CC-10004 were administered in the first study. Oral (gavage) doses of 0 (same vehicle), 5, 25, 75 and 150 mg/kg/day CC-10004 were administered in the second study. Oral (gavage) doses of 0 (same vehicle), 1, 2, and 4 mg/kg/day CC-10004 were administered in the third study. Arteritis was a major toxicity finding noted in these studies. It occurred in a variety of tissues and appeared to be associated with a general inflammatory reaction. The arteritis was described as acute inflammatory cell infiltrate in all layers of the vessel wall,

perivascular edema and hemorrhage, disruption of the elastic lamina, occasional minor areas of necrosis and areas of fibrosis. Other findings included neutrophil and globulin level increase, centrilobular liver hypertrophy, hyperkeratosis and gastritis of the stomach, hemopoiesis in the spleen, and lymphoid hyperplasia in lymph nodes and thymus. Arteritis was noted at doses as low as 5 mg/kg/day. The NOAEL was 4 mg/kg/day for both males and females.

Two 13-week oral toxicity studies were conducted in mice, in which micronized and milled drug substance was compared. In one study oral (gavage) doses of 0 (1% carboxymethylcellulose), 2, 4, 8 and 16 mg/kg/day CC-10004 (micronized, diameter = (b) (4)) were tested. Arteritis in the root of the aorta and the thymus and minor perivascular inflammatory cell infiltration in the lung were noted at 16 mg/kg/day. No arteritis or other toxicities were observed at 8 mg/kg/day or lower. The NOAEL was identified as 8 mg/kg/day. In a second 13-week study, oral (gavage) doses of 0 (same vehicle), 100, 300 and 1000 mg/kg/day CC-10004 (milled; diameter = (b) (4)) were administered to mice for 13 weeks. A treatment-related inflammation manifested by a neutrophilic leukocytosis, lymphopenia and increased acute phase proteins (haptoglobin and CRP) was noted in low, mid and high dose animals during Week 1 but not in Week 13. Treatment-related histopathological findings included inflammatory lesions noted in the lung, heart and aortic root in mid and high dose animals. The NOAEL for this study could be identified as 100 mg/kg/day CC-10004, since the inflammatory effects induced by CC-10004 were transient. The results from human comparative PK study indicated that there was a modest increase in systemic exposure to CC-10004 in the subjects administered micronized drug compared to milled drug; however, the difference in exposure is substantially less in humans compared to what was noted in mice.

In a 6-month oral toxicity study in mice, oral (gavage) doses of 0 (1% carboxymethylcellulose), 10, 100 and 1000 mg/kg/day CC-10004 (milled) were administered. Treatment related mortality was noted in mid and high dose groups. Treatment-related histopathological findings noted in mid and high dose animals included: lesions in the heart that involved inflammation of the aortic root or around the cardiac arteries and in the myocardium, cartilaginous metaplasia of the aortic root along with vascular mineralization, vascular inflammation, hematoma formation and centrilobular hepatocellular hypertrophy of the liver. The NOAEL was identified as 10 mg/kg/day.

In a 4-week oral toxicity study in monkeys, oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 50, 180 and 650 mg/kg/day CC-10004 (micronized) were administered. Increased neutrophil levels and slight increases in liver weight were noted in all drug treated groups. Several occurrences of vasculitis were noted in the mid and high dose groups although these were infrequent and did not follow a dose response. The 50 mg/kg dose might be a NOAEL if the increased neutrophils and slight liver weight increases are not considered adverse.

In a 13-week oral toxicity study in monkeys, oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 25, 85 and 300 mg/kg/day CC-10004 (micronized) were administered. Possible treatment related effects included salivation in low, mid and high dose groups and vomiting in the high dose group. No vasculitis was noted in this study. Inflammatory cell foci in the liver and throughout the body may have also been slightly elevated in drug-treated animals. The NOAEL was identified as 300 mg/kg/day.

In a 12-month oral toxicity study in monkeys, oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 60, 180, and 600 mg/kg/day CC-10004 (milled) were administered. No treatment-related effects on mortality, body weight, ophthalmic parameters, ECG, urinalysis parameters, organ weights, macroscopic parameters, or microscopic parameters were noted in this study. Minor hematology and serum chemistry findings noted in mid and high dose groups were not considered significantly adverse due to the absence of any corresponding histopathological findings. The NOAEL was identified as 600 mg/kg/day.

A special toxicity study was conducted in rats to assess possible biomarkers of inflammation and vasculitis. The animals were treated with oral gavage doses of 0 (vehicle: 0.5% carboxymethylcellulose/0.25% Tween-80), 6 or 10 mg/kg/day CC-10004 for 7 days. CC-10004 caused an acute inflammatory reaction in female rats, characterized by an increase in neutrophils (neutrophilic leukocytosis). A variety of biomarkers where shown to be altered. TNF-α, IL-6, G-CSF, CRP, fibrinogen, MCSF, and VEGF all showed increases during treatment.

CC-10004 in an ethanol:propylene glycol vehicle did not cause dermal irritation in rabbits or guinea pigs, but was classified as a weak sensitizer in a dermal sensitization study in guinea pigs (1 in 20 guinea pigs showed positive signs for dermal sensitization). CC-10004 did not show phototoxic potential in a neutral red uptake assay using Balb/c 3T3 mouse fibroblasts.

In genetic toxicology studies, apremilast tested negative in the Ames assay, an in vitro chromosome aberration assay of human peripheral blood lymphocytes, and an in vivo mouse micronucleus assay. There is no significant concern for its genotoxic potential.

Two 2-year oral carcinogenicity studies were conducted with apremilast (in mice and rats, respectively). No evidence of apremilast-induced tumors was observed in mice at oral doses up to 1000 mg/kg/day or in rats at oral doses up to 20 mg/kg/day in males and 3 mg/kg/day in females, respectively. There is no significant concern for its carcinogenic potential.

In a fertility study of male mice, apremilast at oral (gavage) dosages up to 50 mg/kg/day produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral (gavage) dosages of 0 (vehicle: 1% carboxymethylcellulose), 10, 20, 40, or 80 mg/kg/day. At dosages > 20 mg/kg/day, estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at dosages of 20 mg/kg/day and greater also had increased

incidences of early post-implantation losses. There was no significant effect of apremilast at 10 mg/kg/day.

In an embryo-fetal development study in mice, apremilast was administered at oral (gavage) dosages of 0 (vehicle: 1% carboxymethylcellulose), 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation Day 6 through 15). In a combined fertility and embryo-fetal development study, apremilast was administered at dosages of 0 (same vehicle), 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation Day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in post-implantation loss at doses ≥ 20 mg/kg/day. At doses ≥ 20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at 10 mg/kg/day.

In an embryo-fetal developmental study in cynomolgus monkeys, apremilast was administered at oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation Day 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during Weeks 3 to 4 of dosing in the first trimester, at dose ≥ 50 mg/kg/day. No abortifacient effects were observed at 20 mg/kg/day. Although there was no evidence for a teratogenic effect at doses of 20 mg/kg/day and greater when examined at Day 100, aborted fetuses were not examined.

In a pre- and post-natal developmental study in mice, apremilast was administered to pregnant female mice at oral (gavage) doses of 0 (vehicle: 1% carboxymethylcellulose), 10, 80, or 300 mg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. Dystocia, reduced viability, and reduced birth weights occurred at doses ≥ 80 mg/kg/day. No adverse effects occurred at 10 mg/kg/day. There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to 300 mg/kg/day.

In a single oral dose (10 mg/kg) PK study in lactating mice (~Day 13 of lactation), apremilast was detected in the milk at levels approximately 1.5-times the simultaneous plasma levels at 1 and 6 hr postdose.

In the approved OTEZLA label under NDA 205437, the pregnancy category for apremilast is designated as C. A pregnancy exposure registry is established to monitor and control the risk of OTEZLA.

For this NDA the sponsor proposed the same dosage (MRHD 30 mg BID) and titration schedule as those approved under NDA 205437. Per Dr. Shukla, the systemic exposure to apremilast (AUC value) is fairly similar among subjects with psoriatic arthritis, rheumatoid arthritis, or psoriasis at MRHD (30 mg BID). Therefore, it is acceptable to use the same multiples of human exposure that were presented in the OTEZLA label approved under NDA 205437 in the drug label for this NDA.

The multiples of human exposure based on AUC comparison between NOAELs identified in pivotal toxicology studies and the MRHD are shown in Table 66 in the nonclinical review for NDA 205437 (dated 11/20/2013), which is copied below.

It is noted that in the following table (1) average AUC values of males and females were used for the 6-month mouse study, the 12-month monkey study and the 2-year mouse carcinogenicity study (2) The AUC value used in the pre- and post-natal development study for 10 mg/kg/day dose (4902) is considered an error and should be changed to 9450, same as the value used in the mouse embryo-fetal development study for 10 mg/kg/day dose. The multiples of human exposure should be changed to 1.3X. The multiples of human exposure presented in the approved OTEZLA label under NDA 205437 for the 10 mg/kg/day dose are correct.

This NDA is approvable from a pharmacology/toxicology perspective. No postmarketing requirement is recommended for this NDA.

Table 66: Nonclinical Toxicologically Relevant Exposure Margins

		Adverse Effect	NOAEL (mg/kg/day)	AUC (ng-h/mL)	Exposure Margin+
General Toxicology					
Mouse 6-month study Report CC-10004-TOX-004		Mortality, Vascular Inflammation	**10**	**5728**	**0.77X**
Cyn. Monkey 1 year study Report CC-10004-TOX-005		None	**600**	**34772**	**4.7X**
Carcinogenicity					
Mouse Report CC-10004-TOX-006		None	1000	63952	**8.6X**
Rat Report CC-10004-TOX-007	**male**	None	20	608	**0.08X**
	female	None	3	7721	**1.1X**
Fertility					
Mouse	**male** Report CC-10004-TOX-011	None	50	21040	**2.8X**
	female Report CC-10004-TOX-012	Estrous cyclicity and Mating	10	7407[a]	**1.0X**
		Postimplantation Loss	10	9450[b]	**1.3X**
Embryofetal Development					
Mouse Report CC-10004-TOX-012		Postimplantation Loss	10	9450[b]	**1,3XX**
Cyn. Monkey Report CC-10004-TOX-013		Postimplantation Loss (Abortion)	20	10100	**1.4X**
			50,	15400	**2.1X**
Pre-Postnatal Development*					
Mouse Report CC-10004-TOX-1139	**labor**	Premature Delivery, Dystocia	10	4902*	**0.66X**
	postnatal development	Early Postnatal Mortality	10	4902*	**0.66x**
		Postnatal Development	80	29215*	**3.9X**

+ Exposure margins were based on comparisons between the area under the concentration-time curve (AUC) for a 24 hour period in toxicology studies and the human population PK value of 7440 ng-h/mL for the MRHD of 30 mg BID. The human value was derived from data that included clinical study CC-1004-RA-002 with an AUC_{0-24} of ~7200 ng-h/mL and CC-1004-PSOR-005-PK with an AUC_{0-24} of ~8900 ng-h/mL

* TK was not determined in this study; values from the fertility study, Report CC-10004-TOX-012, were used to determin exposure margins.

[a] AUC at day 14 of premating

[b] AUC at day 15 of gestation

12 Appendix/Attachments

None.

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/s/

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04/01/2014

BARBARA A HILL
04/01/2014