

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OTEZLA safely and effectively. See full prescribing information for OTEZLA.

**OTEZLA® (apremilast) tablets, for oral use**

**Initial US Approval: 2014**

### INDICATIONS AND USAGE

OTEZLA, an inhibitor of phosphodiesterase 4 (PDE4), is indicated for the treatment of adult patients with active psoriatic arthritis (1.1)

### DOSAGE AND ADMINISTRATION

- To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg twice daily according to the following schedule (2.1)
  - Day 1: 10 mg in morning
  - Day 2: 10 mg in morning and 10 mg in evening
  - Day 3: 10 mg in morning and 20 mg in evening
  - Day 4: 20 mg in morning and 20 mg in evening
  - Day 5: 20 mg in morning and 30 mg in evening
  - Day 6 and thereafter: 30 mg twice daily
- Dosage in Severe Renal Impairment:**
  - Recommended dose is 30 mg once daily (2.1)
  - For initial dosage titration, titrate using only morning schedule listed in Table 1 and skip afternoon doses (2.2)

### DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, 20 mg, 30 mg (3)

### CONTRAINDICATIONS

Known hypersensitivity to apremilast or any excipients in formulation (4)

### WARNINGS AND PRECAUTIONS

- Depression:** Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider. Carefully weigh risks and benefits of treatment with OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior. (5.1)
- Weight Decrease:** Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of OTEZLA (5.2)
- Drug Interactions:** Use with strong cytochrome P450 enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, phenytoin) is **not** recommended because loss of efficacy may occur (5.3, 7.1)

### ADVERSE REACTIONS

The most common adverse reactions ( $\geq 5\%$ ) are diarrhea, nausea, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### USE IN SPECIFIC POPULATIONS

**Severe Renal Impairment:** Increased systemic exposure of OTEZLA has been observed, reduction in dose to 30 mg once daily is recommended (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 3/2014

## FULL PRESCRIBING INFORMATION CONTENTS\*

|   |  |
|---|--|
| 1 | <b>INDICATIONS AND USAGE</b>                                   |
|   | 1.1 Psoriatic Arthritis  |
| 2 | <b>DOSAGE AND ADMINISTRATION</b>                               |
|   | 2.1 Dosage in Psoriatic Arthritis                              |
|   | 2.2 Dosage Adjustment in Patients with Severe Renal Impairment |
| 3 | <b>DOSAGE FORMS AND STRENGTHS</b>                              |
| 4 | <b>CONTRAINDICATIONS</b>                                       |
| 5 | <b>WARNINGS AND PRECAUTIONS</b>                                |
|   | 5.1 Depression   |
|   | 5.2 Weight Decrease  |
|   | 5.3 Drug Interactions  |
| 6 | <b>ADVERSE REACTIONS</b>                                       |
|   | 6.1 Clinical Trials Experience in Psoriatic Arthritis          |
| 7 | <b>DRUG INTERACTIONS</b>                                       |
|   | 7.1 Strong CYP450 Inducers                                     |
| 8 | <b>USE IN SPECIFIC POPULATIONS</b>                             |
|   | 8.1. Pregnancy   |
|   | 8.3. Nursing mothers   |
|   | 8.4. Pediatric use   |
|   | 8.5. Geriatric use   |
|   | 8.6. Renal Impairment  |
|   | 8.7. Hepatic Impairment  |

|    |  |
|----|--|
| 10 | <b>OVERDOSAGE</b>  |
| 11 | <b>DESCRIPTION</b>   |
| 12 | <b>CLINICAL PHARMACOLOGY</b>                               |
|    | 12.1. Mechanism of action                                  |
|    | 12.3. Pharmacokinetics                                     |
| 13 | <b>NONCLINICAL TOXICOLOGY</b>                              |
|    | 13.1. Carcinogenesis, mutagenesis, impairment of fertility |
| 14 | <b>CLINICAL STUDIES</b>                                    |
|    | 14.1 Psoriatic Arthritis                                   |
| 16 | <b>HOW SUPPLIED/STORAGE AND HANDLING</b>                   |
| 17 | <b>PATIENT COUNSELING INFORMATION</b>                      |

\*Sections or subsections omitted from the Full Prescribing Information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Psoriatic Arthritis

OTEZLA is indicated for the treatment of adult patients with active psoriatic arthritis.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage in Psoriatic Arthritis

The recommended initial dosage titration of OTEZLA from Day 1 to Day 5 is shown in [Table 1](#). Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

OTEZLA can be administered without regard to meals. Do not crush, split, or chew the tablets.

**Table 1: Dosage Titration Schedule**

| Day 1 | Day 2 |       | 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 |

#### 2.2 Dosage Adjustment in Patients with Severe Renal Impairment

OTEZLA dosage should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance (CL<sub>cr</sub>) of less than 30 mL per minute estimated by the Cockcroft–Gault equation) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. For initial dosage titration in this group, it is recommended that OTEZLA be titrated using only the AM schedule listed in [Table 1](#) and the PM doses be skipped.

### 3 DOSAGE FORMS AND STRENGTHS

OTEZLA is available as diamond shaped, film coated tablets in the following dosage strengths:

- 10 mg pink tablet engraved with “APR” on one side and “10” on the other side
- 20 mg brown tablet engraved with “APR” on one side and “20” on the other side
- 30 mg beige tablet engraved with “APR” on one side and “30” on the other side.

### 4 CONTRAINDICATIONS

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [*see Adverse Reactions (6.1)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Depression

Treatment with OTEZLA is associated with an increase in adverse reactions of depression. During the 0 to 16 weeks placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of patients treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of patients treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated patients (0/495). Depression was reported as serious in 0.2% (3/1441) of patients exposed to OTEZLA, compared to none in placebo treated patients (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of patients while receiving OTEZLA, compared to none in placebo treated patients (0/495). In the clinical trials, two patients who received placebo committed suicide compared to none in OTEZLA treated patients.

Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact

their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

## 5.2 Weight Decrease

During the controlled period of the studies, weight decrease between 5-10% of body weight was reported in 10% (49/497) of patients treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo [see *Adverse Reactions (6.1)*]. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.

## 5.3 Drug Interactions

Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended. [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience in Psoriatic Arthritis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials [Studies PsA-1, PsA-2, and PsA-3] of similar design in adult patients with active psoriatic arthritis [see *Clinical Studies (14.1)*]. Across the 3 studies, there were 1493 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was used over the first 5 days [see *Dosage and Administration (2.1)*]. Placebo patients whose tender and swollen joint counts had not improved by at least 20% were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or 30 mg twice daily at week 16 while OTEZLA patients remained on their initial treatment. Patients ranged in age from 18 to 83 years, with an overall median age of 51 years.

The majority of the most common adverse reactions presented in [Table 2](#) occurred within the first two weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

**Table 2: Adverse Reactions Reported in  $\geq 2\%$  of Patients on OTEZLA 30 mg Twice Daily and  $\geq 1\%$  Than That Observed in Patients on Placebo For Up To Day 112 ( Week 16)**

| Preferred Term                                 | Placebo               |                             | OTEZLA 30 mg BID      |                             |
|--|-----------------------|-----------------------------|-----------------------|-----------------------------|
|  | Day 1 to 5<br>(N=495) | Day 6 to Day 112<br>(N=490) | Day 1 to 5<br>(N=497) | Day 6 to Day 112<br>(N=493) |
|  | n (%) <sup>c</sup>    | n (%)                       | n (%)                 | n (%)                       |
| Diarrhea <sup>a</sup>                          | 6 ( 1.2)              | 8 ( 1.6)                    | 46 ( 9.3)             | 38 ( 7.7)                   |
| Nausea <sup>a</sup>                            | 7 ( 1.4)              | 15 ( 3.1)                   | 37 ( 7.4)             | 44 ( 8.9)                   |
| Headache <sup>a</sup>                          | 9 ( 1.8)              | 11 ( 2.2)                   | 24 ( 4.8)             | 29 ( 5.9)                   |
| Upper respiratory tract infection <sup>b</sup> | 3 ( 0.6)              | 9 ( 1.8)                    | 3 ( 0.6)              | 19 ( 3.9)                   |
| Vomiting <sup>a</sup>                          | 2 ( 0.4)              | 2 ( 0.4)                    | 4 ( 0.8)              | 16 ( 3.2)                   |
| Nasopharyngitis <sup>b</sup>                   | 1 ( 0.2)              | 8 ( 1.6)                    | 1 ( 0.2)              | 13 ( 2.6)                   |
| Abdominal pain upper <sup>b</sup>              | 0 ( 0.0)              | 1 ( 0.2)                    | 3 ( 0.6)              | 10 ( 2.0)                   |

<sup>a</sup> Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache.

<sup>b</sup> Of the reported adverse drug reactions none were serious.

<sup>c</sup> n (%) indicates number of patients and percent.

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:

**Immune system disorders:** Hypersensitivity

**Investigations:** Weight decrease

**Gastrointestinal Disorders:** Frequent bowel movement, Gastroesophageal reflux disease, Dyspepsia

**Metabolism and Nutrition Disorders:** Decreased appetite\*

**Nervous System Disorders:** Migraine

**Respiratory, Thoracic, and Mediastinal Disorders:** Cough

**Skin and Subcutaneous Tissue Disorders:** Rash

\*1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

## 7 DRUG INTERACTIONS

### 7.1 Strong CYP 450 Inducers

Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 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 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  $\geq$  4.0-times the MRHD (on an AUC basis at doses  $\geq$  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  $\geq$  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 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 ( $\geq$ 20 mg/kg/day). At doses of  $\geq$ 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  $\geq$ 4.0-times the MRHD (on an AUC basis at doses  $\geq$ 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.

### 8.4 Pediatric use

The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established.

### 8.5 Geriatric use

Of the 1493 patients who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis patients were 65 years of age and older, including 19 patients 75 years and older. No overall differences were observed in the safety profile of elderly patients  $\geq$  65 years of age and younger adult patients < 65 years of age in the clinical studies.

### 8.6 Renal Impairment

OTEZLA pharmacokinetics were not characterized in subjects with mild (creatinine clearance of 60-89 mL per minute estimated by the Cockcroft–Gault equation) or moderate (creatinine clearance of 30-59 mL per minute estimated by the Cockcroft–Gault equation) renal impairment. The dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockcroft–Gault equation) [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

### 8.7 Hepatic Impairment

Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

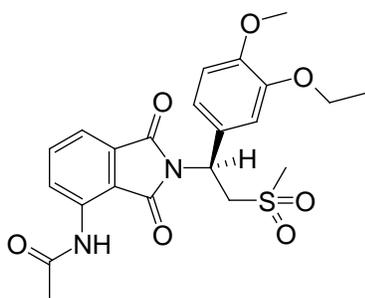
## 10 OVERDOSAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

## 11 DESCRIPTION

The active ingredient in OTEZLA tablets is apremilast. Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. Apremilast is known chemically as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide. Its empirical formula is  $C_{22}H_{24}N_2O_7S$  and the molecular weight is 460.5.

The chemical structure is:



OTEZLA tablets are supplied in 10, 20, and 30 mg strengths for oral administration. Each tablet contains apremilast as the active ingredient and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, iron oxide yellow (20 and 30 mg only) and iron oxide black (30 mg only).

## 12 CLINICAL PHARMACOLOGY

### 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. The specific mechanism(s) by which apremilast exerts its therapeutic action in psoriatic arthritis patients is not well defined.

### 12.3 Pharmacokinetics

#### Absorption

Apremilast when taken orally is absorbed with an absolute bioavailability of ~73%, with peak plasma concentrations ( $C_{max}$ ) occurring at a median time ( $t_{max}$ ) of ~2.5 hours. Co-administration with food does not alter the extent of absorption of apremilast.

#### Distribution

Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution ( $V_d$ ) is 87 L.

#### Metabolism

Following oral administration in humans, apremilast is a major circulating component (45%) followed by inactive metabolite M12 (39%), a glucuronide conjugate of O-demethylated apremilast. It is extensively metabolized in humans with up to 23 metabolites identified in plasma, urine and feces. Apremilast is metabolized by both cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. *In vitro*, CYP metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6.

#### Elimination

The plasma clearance of apremilast is about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 6-9 hours. Following oral administration of radio-labeled apremilast, about 58% and 39% of the radioactivity is recovered in urine and feces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and feces, respectively.

#### Specific Populations

*Hepatic Impairment:* The pharmacokinetics of apremilast is not affected by moderate or severe hepatic impairment.

*Renal Impairment:* In 8 subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC and  $C_{max}$  of apremilast increased by approximately 88% and 42%, respectively. [see *Use in Specific Populations (8.6) and Dosage and Administration (2.2)*].

*Age:* A single oral dose of 30mg apremilast was studied in young adults and elderly healthy subjects. The apremilast exposure in elderly subjects (65 to 85 years of age) was about 13% higher in AUC and about 6% higher in  $C_{max}$  than in young subjects (18 to 55 years of age). [see *Use in Specific Populations (8.5)*].

*Gender:* In pharmacokinetic studies in healthy volunteers, the extent of exposure in females was about 31% higher and  $C_{max}$  was about 8% higher than that in male subjects.

*Race and Ethnicity:* The pharmacokinetics of apremilast in Chinese and Japanese healthy male subjects is comparable to that in Caucasian healthy male subjects. In addition, apremilast exposure is similar among Hispanic Caucasians, non-Hispanic Caucasians, and African Americans.

#### Drug Interactions

*In vitro data:* Apremilast is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 and not an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4. Apremilast is a substrate, but not an inhibitor of P-glycoprotein (P-gp) and is not a substrate or an inhibitor of organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP).

Drug interaction studies were performed with apremilast and CYP3A4 substrates (oral contraceptive containing ethinyl estradiol and norgestimate), CYP3A and P-gp inhibitor (ketoconazole), CYP 450 inducer (rifampin) and frequently co-administered drug in this patient population (methotrexate).

No significant pharmacokinetic interactions were observed when 30 mg oral apremilast was administered with either oral contraceptive, ketoconazole, or methotrexate. Co-administration of the CYP450 inducer rifampin (600 mg once daily for 15 days) with a single oral dose of 30 mg apremilast resulted in reduction of apremilast AUC and  $C_{max}$  by 72% and 43%, respectively. [see *Warnings and Precautions (5.3) and Drug Interactions (7.1)*].

## 13 NONCLINICAL TOXICOLOGY

### 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 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 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  $\geq 1.8$ -times the MRHD ( $\geq 20$  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).

## 14 CLINICAL STUDIES

### 14.1 Clinical Studies in Patients with Psoriatic Arthritis

The safety and efficacy of OTEZLA was evaluated in 3 multi-center, randomized, double-blind, placebo-controlled trials (Studies PsA-1, PsA-2, and PsA-3) of similar design. A total of 1493 adult patients with active PsA ( $\geq 3$  swollen joints and  $\geq 3$  tender joints) despite prior or current treatment with disease-modifying antirheumatic drug (DMARD) therapy were randomized. Patients enrolled in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion of at least 2 cm in diameter was required in Study PsA-3. Previous treatment with a biologic, including TNF-blockers was allowed (up to 10% could be TNF-blocker therapeutic failures). Across the 3 studies, patients were randomly assigned to placebo (n = 496), OTEZLA 20 mg (n = 500), or OTEZLA 30 mg (n = 497) given orally twice daily. Titration was used over the first 5 days [see *Dosage and Administration (2.1)*] Patients were allowed to receive stable doses of concomitant methotrexate [MTX ( $\leq 25$  mg/week)], sulfasalazine [SSZ ( $\leq 2$  g/day)], leflunomide [LEF ( $\leq 20$  mg/day)], low dose oral corticosteroids (equivalent to  $\leq 10$  mg of prednisone a day), and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the trial. Treatment assignments were stratified based on small-molecule DMARD use at baseline in Studies PsA-1, PsA-2 and PsA-3. There was an additional stratification of BSA  $> 3\%$  with psoriasis in study PsA-3. The patients who were therapeutic failures of  $> 3$  agents for PsA (small molecules or biologics), or  $> 1$  biologic TNF blocker were excluded.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. Placebo-controlled efficacy data were collected and analyzed through Week 24. Patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo non-responders were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or 30 mg twice daily following the titration schema [see *Dosage and Administration (2.1)*]. OTEZLA patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomized to either 20 mg twice daily or 30 mg twice daily.

Patients with subtypes of PsA were enrolled across the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (27.0%), distal interphalangeal (DIP) joint arthritis (6.0%), arthritis mutilans (3.0%), and predominant spondylitis (2.1%). The median duration of PsA disease was 5 years. Patients received concomitant therapy with at least one DMARD (65.0%), MTX (55.0%), SSZ (9.0%), LEF (7.0%), low dose oral corticosteroids (14.0%), and NSAIDs (71.0%). Prior treatment with small-molecule DMARDs only was reported in 76.0% of patients and prior treatment with biologic DMARDs was reported in 22.0% of patients, which includes 9.0% who had failed prior biologic DMARD treatment.

#### Clinical Response in Patients with Psoriatic Arthritis

The percent of patients achieving ACR 20, 50 and 70 responses in Studies PsA-1, PsA-2, and PsA-3 are presented in [Table 3](#) below. OTEZLA  $\pm$  DMARDs, compared with Placebo  $\pm$  DMARDs resulted in a greater improvement in signs and symptoms of psoriatic arthritis as demonstrated by the proportion of patients with an ACR 20 response at Week 16.

**Table 3: Proportion of Patients with ACR Responses in Studies PsA-1, PsA-2 and PsA-3**

|                           | PsA 1                      |   | PsA 2                      |   | PsA 3                      |   |
|---------------------------|----------------------------|---|----------------------------|---|----------------------------|---|
|                           | Placebo<br>$\pm$<br>DMARDs | Otezla<br>30 mg<br>twice daily<br>$\pm$<br>DMARDs | Placebo<br>$\pm$<br>DMARDs | Otezla<br>30 mg<br>twice daily<br>$\pm$<br>DMARDs | Placebo<br>$\pm$<br>DMARDs | Otezla<br>30 mg<br>twice daily<br>$\pm$<br>DMARDs |
| N <sup>a</sup>            | N = 168                    | N = 168   | N = 159                    | N = 162   | N = 169                    | N = 167   |
| <b>ACR 20<br/>Week 16</b> | 19%                        | 38% <sup>b</sup>                                  | 19%                        | 32% <sup>b</sup>                                  | 18%                        | 41% <sup>b</sup>                                  |
| <b>ACR 50<br/>Week 16</b> | 6%                         | 16%   | 5%                         | 11%   | 8%                         | 15%   |

|                |    |    |    |    |    |    |
|----------------|----|----|----|----|----|----|
| <b>ACR 70</b>  |    |    |    |    |    |    |
| <b>Week 16</b> | 1% | 4% | 1% | 1% | 2% | 4% |

<sup>a</sup>N is number of randomized and treated patients

<sup>b</sup>Statistically significantly different from placebo (p<0.05)

OTEZLA 30 mg twice daily resulted in improvement for each ACR component, compared to placebo at Week 16 in Study PsA-1 (Table 4). Consistent results were observed in Studies PsA-2 and PsA-3.

**Table 4: ACR Components Mean Change from Baseline at Week 16 in Study PsA- 1**

|  | Placebo<br>(N=168) | OTEZLA 30 mg<br>twice daily<br>(N=168) |
|--|--------------------|--|
| Number of tender joints <sup>a</sup>                           |                    |  |
| Sample Size  | 166                | 164                                    |
| Baseline   | 23                 | 23                                     |
| Mean Change at Week 16   | -2                 | -7                                     |
| Number of swollen joints <sup>b</sup>                          |                    |  |
| Sample Size  | 166                | 164                                    |
| Baseline   | 13                 | 13                                     |
| Mean Change at Week 16   | -2                 | -5                                     |
| Patient's assessment of pain <sup>c</sup>                      |                    |  |
| Sample Size  | 165                | 159                                    |
| Baseline   | 61                 | 58                                     |
| Mean Change at Week 16   | -6                 | -14                                    |
| Patient's global assessment of disease activity <sup>c</sup>   |                    |  |
| Sample Size  | 165                | 159                                    |
| Baseline   | 59                 | 56                                     |
| Mean Change at Week 16   | -3                 | -10                                    |
| Physician's global assessment of disease activity <sup>c</sup> |                    |  |
| Sample Size  | 158                | 159                                    |
| Baseline   | 55                 | 56                                     |
| Mean Change at Week 16   | -8                 | -19                                    |
| HAQ-DI <sup>d</sup> score                                      |                    |  |
| Sample Size  | 165                | 159                                    |
| Baseline   | 1.2                | 1.2                                    |
| Mean Change at Week 16   | -0.09              | -0.2                                   |
| CRP <sup>e</sup>   |                    |  |
| Sample Size  | 166                | 167                                    |
| Baseline   | 1.1                | 0.8                                    |
| Mean Change at Week 16   | 0.1                | -0.1                                   |

Mean changes from baseline are least square means from analyses of covariance.

<sup>a</sup> Scale 0-78

<sup>b</sup> Scale 0-76

<sup>c</sup> VAS = Visual Analog Scale; 0 = best, 100 = worst

<sup>d</sup> HAQ-DI = Health Assessment Questionnaire-Disability Index; 0 = best, 3 = worst; measures the subject's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

<sup>e</sup> CRP = C-reactive protein; Reference range 0-0.5 mg/dL

\* N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.

Treatment with OTEZLA resulted in improvement in dactylitis and enthesitis in patients with pre-existing dactylitis or enthesitis.

### Physical Function Response

OTEZLA 30 mg twice daily demonstrated a greater improvement compared to placebo in mean change from baseline for the Health Assessment Questionnaire Disability Index (HAQ-DI) score at Week 16 [-0.244 vs. -0.086, respectively; 95% CI for the difference was (-0.26, -0.06)] in Study PsA-1. The proportions of HAQ-DI responders ( $\geq 0.3$  improvement from baseline) at Week 16 for the OTEZLA 30

mg twice daily group were 38%, compared to 27%, for the placebo group in Study PsA-1. Consistent results were observed in Studies PsA-2 and PsA-3

## 16 HOW SUPPLIED/STORAGE AND HANDLING

OTEZLA is available as diamond shaped film coated tablets in the following dosage strengths: 10 mg pink tablet engraved with “APR” on one side and “10” on the other side; 20 mg brown tablet engraved with “APR” on one side and “20” on the other side; 30 mg beige tablet engraved with “APR” on one side and “30” on the other side.

Tablets are supplied in the following strengths and package configurations

| Package configuration | Tablet strength  | NDC code     |
|-----------------------|--|--------------|
| Bottles of 60         | 30 mg  | 59572-630-06 |
| Two week starter pack | 13-tablet blister titration pack containing: 10 mg, 20 mg, and 30 mg tablets with an additional (14) 30 mg tablets | 59572-630-27 |
| 28 count carton       | 2-30mg blister cards containing (14) 30 mg tablets   | 59572-630-28 |

### Storage and Handling

Store tablets below 30 °C (86°F).

## 17 PATIENT COUNSELING INFORMATION

### • Depression

Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur. [see *Warnings and Precautions (5.1)*]

### • Weight Decrease

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered. [see *Warnings and Precautions (5.2)*]

### • Drug Interactions

The use of strong cytochrome P450 enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended. [see *Warnings and Precautions (5.3)*, *Drug Interactions (7.1)*, and *Clinical Pharmacology (12.3)*].

- Instruct patients to take OTEZLA only as prescribed.
- Advise patients OTEZLA can be taken with or without food.
- Advise patients that the tablets should not be crushed, split, or chewed.
- Advise patients about the side effects associated with OTEZLA. [See *Adverse Reactions (6.1)*].

Manufactured for: Celgene Corporation  
Summit, NJ 07901

OTEZLA<sup>®</sup> is a registered trademarks of Celgene Corporation.

Pat. www.celgene.com

©2014 Celgene Corporation, All Rights Reserved.

APRPI.001 03/14