PRODUCT MONOGRAPH

[Pr]MAR-APREMILAST

apremilast tablets

10 mg, 20 mg, and 30 mg

Selective Immunosuppressant

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Apremilast Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets: 10 mg, 20 mg and 30 mg	Anhydrous Lactose, Croscarmellose sodium Microcrystalline cellulose, Magnesium stearate Film coat contains: ferrosoferric oxide/black iron oxide (for 30mg), HPMC/ hypromellose, iron oxide red, iron oxide yellow (for 20 mg and 30 mg), lactose monohydrate, titanium dioxide, triacetin)

INDICATIONS AND CLINICAL USE

- **Plaque Psoriasis**

  MAR-APREMILAST (apremilast) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

  Limitations of Use:

  MAR-APREMILAST has not been studied and is therefore not indicated in combination with other systemic (conventional or biologic) therapies or phototherapy for psoriasis.

- **Psoriatic Arthritis**

  MAR-APREMILAST (apremilast), alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response, intolerance, or contraindication to a prior disease-modifying anti-rheumatic drug (DMARD).

- **Behçet's Disease**

  MAR-APREMILAST is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy.

Geriatrics (≥ 65 years of age):

Patients 65 years of age or older may be at a higher risk of complications of severe diarrhea, nausea and vomiting caused by MAR-APREMILAST (see **WARNINGS AND PRECAUTIONS, Gastrointestinal**). No overall differences were observed in the efficacy of apremilast between elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies. Clinical data in patients of 75 years of age or older are limited. MAR-APREMILAST should be used with caution in patients ≥ 65 years of age.

Pediatrics (< 18 years of age):

The safety and effectiveness of MAR-APREMILAST in pediatric patients have not been established. MAR-APREMILAST should not be used in this patient population.

CONTRAINDICATIONS

MAR-APREMILAST (apremilast) is contraindicated in:

- Patients with known hypersensitivity to the active substance or to any of the excipients. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**
- Pregnancy
- Women who are breastfeeding.

WARNINGS AND PRECAUTIONS

Cardiovascular

Tachyarrhythmia

There have been uncommon reports of tachyarrhythmia, including atrial fibrillation, in Phase 2/3 studies. The incidence of tachyarrhythmia events was 0.2% for placebo and 0.6% for apremilast 30 mg BID patients. Of these, atrial fibrillation had an incidence of 0.1% for placebo and 0.3% for apremilast patients. Use with caution in patients with a history of tachyarrhythmia or conditions that can be worsened by increases in heart rate (e.g. ischemic heart disease or congestive heart failure) (see **ACTION AND CLINICAL PHARMACOLOGY**, **Cardiac Electrophysiology**).

Endocrine and Metabolic

Weight loss

In Phase 3 studies, clinically significant weight loss was observed. Weight decreases of greater than 5% of baseline body weight were observed more frequently in women than in men.

Patients treated with MAR-APREMILAST should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of MAR-APREMILAST should be considered.

Gastrointestinal

Diarrhea, Nausea and Vomiting

Physicians should discuss with patients and/or caregivers the potential for diarrhea, vomiting and nausea when taking MAR-APREMILAST.

In clinical trials, apremilast was associated with severe adverse reactions of diarrhea, nausea or vomiting (incidence 0.11%). In post-marketing reports, apremilast was associated with reports of severe diarrhea, nausea, or vomiting which in some cases, led to hospitalization (see **ADVERSE REACTIONS**). Most events occurred within the first few weeks of treatment.

Dosing of MAR-APREMILAST should be suspended or discontinuation considered if patients develop severe adverse reactions of diarrhea, nausea or

vomiting.

Elderly (≥ 65 years of age) or patients taking medication or with intercurrent conditions (such as gastrointestinal illness) that lead to volume depletion or hypotension may be at a higher risk of complications, such as dehydration, hypotension and electrolyte imbalance. Appropriate precaution should be taken to limit the risk of volume depletion when administering MAR-APREMILAST in these patients.

Lactose

MAR-APREMILAST tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take MAR-APREMILAST.

Immune

Apremilast has not been studied in patients with severe immunological diseases, severe acute infectious diseases, or psoriasis patients treated with immunosuppressive medicinal products. Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster is limited. MAR-APREMILAST should be used with caution in these patient populations. MAR-APREMILAST is not recommended in combination with potent immunosupressants, including biological therapies and cyclosporine (see **DRUG INTERACTIONS, DOSAGE AND ADMINISTRATION**)

Neurologic

Apremilast was associated with an increased incidence of headache and migraine during the placebo-controlled period (see **ADVERSE REACTIONS**).

Physicians should discuss the potential for headache/migraine with MAR-APREMILAST with their patients and/or caregivers.

Psychiatric

Depression

In Phase 3 psoriasis studies, treatment with apremilast was associated with an increase in adverse reactions of depression during the placebo-controlled period. The incidence of depression or depressed mood was 1.44% for apremilast 30 mg BID and 0.48% for placebo. In Phase 2/3 studies, the incidences of serious events of depression or of suicidal ideation were < 0.5% in patients treated with apremilast 30 mg BID. Similar incidences were observed in the psoriatic arthritis and Behçet's disease studies.

Before using MAR-APREMILAST in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with MAR-APREMILAST in such patients. Physicians should discuss psychiatric adverse events with their patients and/or caregivers. Patients and/or caregivers should be instructed to notify the physician if these events do occur.

Renal

A dosage reduction of MAR-APREMILAST to 30 mg once daily is recommended in patients with severe renal impairment (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY)**. The safety and efficacy of apremilast in patients with severe renal impairment have not been evaluated. Therefore use with caution in these patients. Assessment of renal function is recommended prior to initiation of MAR-APREMILAST tablets.

Special Populations

Pregnant Women

There are no adequate and well controlled studies of apremilast in pregnant women. MAR-APREMILAST is contraindicated during pregnancy and should not be used in women attempting to conceive (see **CONTRAINDICATIONS**).

Enhanced Surveillance Program for Adverse Pregnancy Outcomes

An Enhanced Surveillance Program for Adverse Pregnancy Outcomes has been established to collect information about the effect of MAR-APREMILAST exposure during pregnancy. Physicians are encouraged to enroll pregnant women in the Enhanced Surveillance Program for Adverse Pregnancy Outcomes by calling 1-855-627-2261 or visiting www.marcanpharma.com.

Nursing Women

It is not known whether apremilast, or its metabolites, are excreted in human milk. Therefore, MAR-APREMILAST is contraindicated in nursing women (see **CONTRAINDICATIONS**).

Apremilast was detected in milk of lactating mice. An increased incidence of peri- and post-natal pup mortality was observed at doses ≥ 80 mg/kg/day (≥4.0-fold clinical exposure) (see **TOXICOLOGY**).

Pediatrics (< 18 years of age)

The safety and effectiveness of apremilast in pediatric patients have not been established. Therefore, MAR-APREMILAST should not be used in this patient population.

Geriatrics (≥ 65 years of age)

Patients 65 years of age or older may be at a higher risk of complications of severe diarrhea, nausea and vomiting caused by MAR-APREMILAST (see **WARNINGS AND PRECAUTIONS, Gastrointestinal**). Clinical data in patients of 75 years of age or older are limited. MAR-APREMILAST tablets should be used with caution in patients ≥ 65 years of age.

Monitoring and Laboratory Tests

Weight

Patients treated with MAR-APREMILAST should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of MAR-APREMILAST should be considered.

Renal Function

Assessment of renal function is recommended prior to initiation of MAR-APREMILAST.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In the Phase 3 psoriasis studies, the most common adverse reactions (≥ 5%) were diarrhea, nausea, upper respiratory tract infection, tension headache, and headache

(Table 1). The incidences of these events were higher in females than males. In particular, during the placebo-controlled period, nausea was experienced by 29.7% of women (compared to 9.9% of males), diarrhea by 24.0% of women (compared to 14.6% of men), vomiting by 7.9% of women (compared to 1.6% of men), and tension headache by 11.5% of women (compared to 5.2% of men). The majority of the adverse reactions of diarrhea, nausea, tension headache, and headache began within the first two weeks of treatment, and nearly half of these adverse reactions resolved within 2 weeks of onset. These events were mostly mild in intensity with the incidence of severe events ranging from 0.1 % - 0.6 %.

In the period of exposure to apremilast in the pivotal psoriasis trials, the most common serious adverse event for patients exposed to apremilast was nephrolithiasis (0.3%). The most common adverse reactions leading to discontinuation for patients taking apremilast were nausea, diarrhea, psoriasis, headache, and vomiting.

In the Phase 3 psoriatic arthritis studies, diarrhea, nausea, and headache were the most commonly reported (≥ 5%) adverse drug reactions. The incidences of these events were higher in females than males. More than half of these events occurred in the first 15 days of exposure and more than half of these resolved within the first 30 days. These events were mostly mild to moderate in intensity in the placebo-controlled period with the incidence of severe episodes ranging from 0.2% - 0.6%.

In the period of exposure to apremilast in the pivotal psoriatic arthritis trials, the most common serious adverse event for patients exposed to apremilast was psoriatic arthropathy (0.6%), of which 6 of 7 cases were women. The most common adverse reactions leading to discontinuation for patients taking apremilast were nausea (2.2%), diarrhea (2.2%), and headache (1.5%).

In the placebo-controlled period of the Phase 3 Behçet's disease study, diarrhea, nausea, headache and upper respiratory tract infection were the most commonly reported (≥ 10%) adverse drug reactions. Most of these were mild to moderate in severity. Serious adverse events that were observed in patients exposed to apremilat during the placebo-controlled period, were Behçet's syndrome (1%), migraine (1%), and soft tissue injury (1%).The most common adverse reactions leading to discontinuation for patients taking apremilast were headache (1%), upper abdominal pain (1%), Behçet's syndrome (1%), nausea (1%) and vomiting (1%).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice, and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In two 52-week Phase 3 pivotal trials in psoriasis (Studies ESTEEM 1 and ESTEEM 2) (see **CLINICAL TRIALS)**, 418 subjects were randomized to receive placebo, and 832 subjects to receive at least one dose of apremilast 30 mg BID. Including placebo subjects switched to receive apremilast 30 mg BID at Week 16, a total of 1184 subjects were exposed to apremilast 30 mg BID. A total of 564 subjects received apremilast 30 mg BID for at least 52 weeks. Patients ranged in age from 18 to 83 years, with an overall median age of 46 years.

Table 1. Treatment-Emergent Adverse Events With Subject Incidence ≥ 2% in Any Treatment Group and the Incidence in apremilast Exceeded Placebo During Weeks 0-16 (PSOR Phase 3 Data Pool)

	Subjects as Initially Treated at Week 0	
	Placebo (N = 418)	Apremilast 30 BID (N = 832)
System organ class Preferred Term	n (%)	n (%)
Gastrointestinal disorders		
Diarrhea	28 (6.7)	148 (17.8)
Nausea	28 (6.7)	138 (16.6)
Vomiting	7 (1.7)	31 (3.7)
Dyspepsia	4 (1.0)	25 (3.0)
Abdominal discomfort	6 (1.4)	18 (2.2)
Frequent bowel movements	1 (0.2)	17 (2.0)
Abdominal pain	6 (1.4)	17 (2.0)
Abdominal pain upper	4 (1.0)	18 (2.2)
Infections and infestations		
Upper respiratory tract infection	27 (6.5)	70 (8.4)
Nasopharyngitis	29 (6.9)	61 (7.3)
Sinusitis	6 (1.4)	18 (2.2)
Nervous system disorders		
Tension headache	14 (3.3)	61 (7.3)
Headache	14 (3.3)	48 (5.8)
Migraine	4 (1.0)	17 (2.0)
General disorders and administration site conditions		
Fatigue	6 (1.4)	25 (3.0)
Metabolism and nutrition disorders		
Decreased appetite	4 (1.0)	23 (2.8)
Musculoskeletal and connective tissue disorders		
Back pain	4 (1.0)	20 (2.4)
Psychiatric disorders		
Insomnia	4 (1.0)	20 (2.4)

Apremilast was evaluated in 3 52-week, Phase 3 pivotal trials (Studies PALACE 1, PALACE 2, and PALACE 3) of similar design in adult patients with active psoriatic arthritis. Across the 3 studies, 1493 patients were randomized equally to placebo, Apremilast 20 mg twice daily or apremilast 30 mg twice daily. Patients ranged in age from 18 to 83 years, with an overall median age of 51 years.

Table 2. Treatment-Emergent Adverse Events With Subject Incidence ≥ 1% in Any Treatment Group and where the Incidence in Apremilast Exceeded Placebo by ≥ 0.5% During Weeks 0-16 (PsA Phase 3 Data Pool)

System organ class Preferred Term	Patients as Initially Treated at Week 0	
	Placebo n = 495 n (%)	Apremilast 30 BID n = 497 n (%)
Cardiac Disorders		
Palpitations	1 (0.2)	5 (1.0)
Gastrointestinal Disorders		
Diarrhea[a]	14 (2.8)	83 (16.7)
Nausea [a]	22 (4.4)	76 (15.3)
Vomiting[a]	4 (0.8)	19 (3.8)
Abdominal pain upper	1 (0.2)	13 (2.6)
Abdominal pain	8 (1.6)	13 (2.6)
Dyspepsia	6 (1.2)	11 (2.2)
Frequent Bowel Movements	0 (0.0)	8 (1.6)
Gastroesophageal reflux disease	1 (0.2)	7 (1.4)
Flatulence	1 (0.2)	7 (1.4)
General Disorders and Administrative Site Conditions		
Fatigue	5 (1.0)	9 (1.8)
Infections and Infestations		
Upper Respiratory Tract Infection	12 (2.4)	21 (4.2)
Nasopharyngitis	9 (1.8)	14 (2.8)
Influenza	1 (0.2)	5 (1.0)
Investigations		
Weight Decreased	2 (0.4)	7 (1.4)
Nervous System Disorders		
Headache[a]	20 (4.0)	52 (10.5)
Dizziness	6 (1.2)	11 (2.2)
Migraine	0 (0.0)	9 (1.8)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2 (0.4)	8 (1.6)

[a] One patient experienced a serious adverse drug reaction of nausea and vomiting in apremilast 30 mg twice daily; 1 patient treated with apremilast 20 mg twice daily experienced a serious adverse drug reaction of diarrhea. One patient treated with apremilast 30 mg twice daily experienced a serious adverse drug reaction of headache.

Apremilast was evaluated in a Phase 3, multicenter, randomized, placebo-controlled study (RELIEF) (see **CLINICAL TRIALS**) in adult patients with Behçet's disease with active oral ulcers. A total of 207 patients were randomized to receive apremilast 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days. After Week 12, all patients received treatment with apremilast 30 mg twice daily. Patients ranged in age from 19 to 72, with a mean age of 40 years.

Table 3. Treatment-Emergent Adverse Events With Subject Incidence ≥5% in Any Treatment Group, and Where the Incidence in Apremilast Exceeded Placebo by ≥ 1%, During Weeks 0 - 12) (RELIEF Study)

System organ class Preferred Term	Patients as Initially Treated at Week 0	
	Placebo (N=103) n (%)	Apremilast 30 BID (N=104) n (%)
Diarrhea[a]	21 (20.4)	43 (41.3)
Nausea[a]	11 (10.7)	20 (19.2)
Headache	11 (10.7)	15 (14.4)
Upper respiratory tract infection	5 (4.9)	12 (11.5)
Abdominal pain upper	2 (1.9)	9 (8.7)
Vomiting[a]	2 (1.9)	9 (8.7)
Back pain	6 (5.8)	8 (7.7)
Viral upper respiratory tract infection	5 (4.9)	7 (6.7)
Arthralgia	3 (2.9)	6 (5.8)

[a] There were no serious adverse reactions of diarrhea, nausea or vomiting.

Less Common Clinical Trial Adverse Drug Reactions

Adverse reactions reported in less than 1% of patients on apremilast in clinical studies for psoriatic arthritis and at least 0.5% greater than placebo, or in less than 2% of patients on apremilast in clinical studies (including extension phases) in plaque psoriasis and other patient populations; or in less than 5% of patients on apremilast in clinical studies in Behçet's disease and at least 1% greater than placebo

- **Cardiac disorders:** Palpitations
- **Gastrointestinal Disorders:** Abdominal distension, Abdominal pain, Gastroesophageal reflux disease
- **Immune System Disorders:** Hypersensitivity
- **Infections and Infestations:** Bronchitis, Influenza, Pharyngitis, Pneumonia, Rhinitis
- **Investigations:** Weight decrease
- **Metabolism and nutrition Disorders:** Decreased appetite

- **Musculoskeletal and Connective Tissue Disorders:** Arthralgia, Muscle spasms, Myalgia
- **Nervous System Disorders:** Paresthesia, Sinus headache
- **Psychiatric Disorders:** Depression
- **Respiratory, Thoracic, and Mediastinal Disorders:** Cough
- **Skin and Subcutaneous Tissue Disorders:** Rash

The long-term safety profile of apremilast treatment was comparable to that observed with apremilast during the placebo-controlled period of the PsA/PSOR/BD studies.

Post-Market Adverse Drug Reactions

Gastrointestinal: Severe diarrhea, nausea and/or vomiting, gastrointestinal hemorrhage (see **WARNINGS AND PRECAUTIONS, Gastrointestinal**).

Skin and Subcutaneous Tissue Disorders: urticaria, angioedema.

DRUG INTERACTIONS

Overview

In vitro, 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, weak 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). Therefore, apremilast is unlikely to result in clinically relevant drug-drug interactions when co-administered with drugs that are substrates or inhibitors of these CYP enzymes or transporters.

Drug-Drug Interactions

No significant interactions were observed when 30 mg oral apremilast was administered with ketoconazole (CYP3A4 inhibitor), methotrexate and oral contraceptives (CYP3A4 substrate) containing ethinyl estradiol and norgestimate.

Combination with:

Strong CYP3A4 Inducers

Apremilast exposure (AUC) and maximal concentrations (C_{max}) were decreased by 72% and 43% when co-administered with CYP3A4 inducer rifampin, and may result in reduced clinical efficacy of apremilast. Hence co-administration of rifampin or other CYP3A4 inducers (e.g. phenobarbital, carbamazepine, phenytoin) along with MAR-APREMILAST is not recommended (Table 3).

Cyclosporine

MAR-APREMILAST has not been evaluated and is not indicated in combination with potent immunosuppressive drugs (e.g. cyclosporine, tacrolimus). MAR-APREMILAST is not recommended in combination with potent immunosuppressive drugs (see **INDICATIONS AND CLINICAL USE**, **Limitations of Use; WARNINGS AND PRECAUTIONS**, **Immune**).

Biological Therapeutics

MAR-APREMILAST has not been evaluated and is not indicated to be used in combination with biological therapeutics, for psoriasis or psoriatic arthritis, such as TNF antagonists and anti-IL-12/23 p40 antibodies. MAR-APREMILAST is not recommended in combination with these biological therapeutics (see **INDICATIONS AND CLINICAL USE**, **Limitations of Use**; **WARNINGS AND PRECAUTIONS**, **Immune**).

Table 3. Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Rifampin	CT	Co-administration of the strong CYP3A4 inducer rifampin (600 mg once daily for 15 days), with a single oral dose of 30 mg apremilast, resulted in reduction of apremilast's AUC and C_{max} by approximately 72% and 43%, respectively and may result in reduced clinical response ofapremilast.	MAR-APREMILAST is NOT RECOMMENDED for co-administration along with rifampin or other potent CYP3A4 inducers.
Ketoconazole	CT	Co-administration of ketoconazole (a strong CYP3A4 inhibitor, 400 mg QD) with a single dose (20 mg) of apremilast increased mean apremilast AUC $_{0-\infty}$ and C_{max} by approximately 36 % and by 5%, respectively, which is not clinically meaningful.	MAR-APREMILAST can be co- administered with a potent CYP3A4 inhibitor like ketoconazole. No dosage adjustment of Apremilast is required on co-administration.
Methotrexate	CT	There was no pharmacokinetic drug-drug interaction between apremilast (30 mg BID) and methotrexate (between 7.5 mg and 20 mg once a week) in psoriatic arthritis patients.	In psoriasis, the efficacy and safety of MAR-APREMILAST in combination with methotrexate has not been established and is therefore NOT INDICATED.
oral contraceptives	CT	There was no pharmacokinetic drug-drug interaction between apremilast (30 mg BID) and oral contraceptives containing ethinyl estradiol (0.035 mg) and norgestimate (0.18 mg/0.215 mg/0.25mg).	MAR-APREMILAST can be taken with oral contraceptives without clinically relevant drug-drug interaction. No dosage adjustment of MAR-APREMILAST is required on co-administration.

Legend: AUC = Area under curve; CT = Clinical Trial; CYP = Cytochrome P450.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

St John's Wort is a CYP3A4 inducer, and co-administration with MAR-APREMILAST may result in loss of efficacy or reduced clinical response, and is not recommended.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Population pharmacokinetic studies demonstrated that apremilast pharmacokinetics were similar between smokers and non-smokers.

DOSAGE AND ADMINISTRATION

Dosing Considerations

MAR-APREMILAST has not been evaluated and is therefore not indicated in combination with potent immunosuppressants or biological therapeutics for psoriasis, psoriatic arthritis or Behçet's disease such as tumor necrosis factor (TNF) antagonists and anti-IL-12/23 p40 antibodies (see **INDICATIONS AND CLINICAL USE**, **Limitations of Use**).

In Behçet's disease, MAR-APREMILAST should be used by physicians who have knowledge of Behçet's disease and who have fully familiarized themselves with the efficacy and safety profile of apremilast.

Recommended Dose and Dosage Adjustment

Recommended adult dose (≥ 18 years of age and older):

The recommended dose of MAR-APREMILAST is 30 mg twice daily. MAR-APREMILAST tablets can be taken with or without food. An initial titration schedule is required, as shown below in Table 4, to reduce the risk of gastrointestinal symptoms.

Table 4. Dose Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6	
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

Special Populations

Pediatrics (< 18 years of age)

The safety and effectiveness of MAR-APREMILAST in pediatric patients have not been established. Therefore, MAR-APREMILAST should not be used in this patient population.

Geriatrics (≥ 65 years of age)

No dosage adjustment is necessary for elderly patients (≥ 65 years of age). Due to limited data available in very elderly patients (≥ 75 years of age), MAR-APREMILAST should be used with caution in this patient population.

Hepatic Impairment

No dosage adjustment is necessary in patients with moderate and severe hepatic impairment.

Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment.

The safety and efficacy of apremilast have not been evaluated in patients with severe renal impairment. The maximal recommended dose of apremilast is 30 mg once daily in

patients with severe renal impairment (creatinine clearance [CLcr] of less than 30 mL per minute estimated by the Cockroft–Gault equation). For initial dosage titration, titrate using only the morning dose (AM dose) in Table 4 and skip the afternoon dose (PM dose). Continue thereafter at 30 mg once daily (see **WARNINGS AND PRECAUTIONS**, **Renal**).

Missed Dose

Patients should be advised that if they miss a dose of MAR-APREMILAST, they should continue with the next tablet at the usual time. Patients should not take a double dose to make up for a missed dose.

Administration

MAR-APREMILAST tablets should be swallowed whole. The tablets should not be crushed, split or chewed.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Apremilast, a small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Phosphodiesterase 4 inhibition elevates intracellular cAMP levels, thereby reducing the inflammatory response by modulating the expression of tumor necrosis factor-α (TNF-α), interleukin-23 (IL-23), IL-17 and IL-10.

Pharmacodynamics

In clinical trials in patients with psoriasis, apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro -inflammatory genes, including those for inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-23p19, IL-17A, IL-22 and IL-8.

Cardiac Electrophysiology

A double-blind, placebo- and positive-controlled, randomized, multiple-dose, four period crossover study was performed to investigate the effects of apremilast on ECG interval parameters in healthy male volunteers (N=60). Apremilast was tested at a therapeutic dose (30 mg BID on days 1-4 and 30 mg QD on day 5) and a supratherapeutic dose (50 mg BID on days 1-4 and 50 mg QD on day 5). Apremilast 30 mg and 50 mg did not have noteworthy effects on the QTc, QRS, or PR intervals on day 5 of treatment. For the therapeutic 30 mg treatment arm, heart rate was increased from 0.5 h- 4 h post-dosing on day 5, with a maximum mean difference from placebo of 3.4 bpm (90% CI: 1.1, 5.6) at 2 h. For the supratherapeutic 50 mg BID treatment arm, heart rate was increased from 0.5 h-4 h and at 23 h post-dosing on day 5, with a maximum mean difference from placebo of 4.9 bpm (90% CI: 3.3, 6.6) at 3 h (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular)**.

Pharmacokinetics

Table 5. Summary of Apremilast Pharmacokinetic Parameters after 30 mg Twice Daily in Psoriasis and Psoriatic Arthritis Subjects

Indication and Dose	C_{max} (ng/mL)	$t_{½}$ (h)	AUC_{0-T} (ng•h/mL)	CL/F (L/h)	V/F (L)
Psoriasis 30 mg BID (N=166)	382 (36.4)	9.67 (22.3)	3425 (42.0)	8.76 (41.2)	122 (24.4)
Psoriatic Arthritis 30 mg BID (N = 61)	423 (42.6)	8.88 (25.4)	3720 (49.6)	8.07 (36.5)	103 (26.1)

Legend: AUC= Area under curve; BID = Twice daily; C_{max} = Maximum concentration; CL/F = apparent clearance; $t_{1/2}$ = terminal half-life; V/F = apparent volume of distribution
Note: Values are displayed as geometric mean (coefficient of variation [%]).

Absorption:

Apremilast is well absorbed, with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics are linear, with a dose-proportional increase in systemic exposure and less than dose proportional increase in C_{max} between the dose range of 10 to 100 mg daily in healthy volunteers. Co-administration with food does not alter the extent of absorption (AUC and C_{max}), but slightly delays time to maximum concentration (t_{max}) of apremilast by 0.75 hour; therefore, apremilast can be administered with or without food.

Distribution:

Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution (Vd) is 87 L, indicative of extravascular distribution.

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.

Excretion:

The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 6-9 hours. Following oral administration of radiolabeled 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.

Special Populations and Conditions

Pediatrics

The safety and effectiveness of MAR-APREMILAST in pediatric patients have not been established and should not be used in this patient population (see **INDICATIONS AND CLINICAL USE**, **WARNINGS AND PRECAUTIONS**, **Special Populations)**.

Geriatrics

A single oral dose of 30 mg 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 younger subjects (18 to 55 years of age). Age did not have a clinically meaningful effect on the pharmacokinetics of apremilast (see **INDICATIONS AND CLINICAL USE**, **WARNINGS AND PRECAUTIONS**, **Special Populations)**.

Sex

In a pharmacokinetic study of apremilast in healthy volunteers, the exposure ($AUC_{0-\infty}$) and maximal concentrations (C_{max}) in females were 31% and 8% higher than in male subjects. Sex did not have a clinically meaningful effect on the pharmacokinetics of apremilast.

Race

The pharmacokinetics of apremilast in Chinese and Japanese healthy male subjects is comparable to that in Caucasian healthy male subjects. Pharmacokinetic analyses based on the pooled data from Phase 1 studies showed that apremilast exposure is also similar among Hispanic Caucasians, non -Hispanic Caucasians, and African Americans. The exposure ($AUC_{0-\infty}$ or $AUC_{0-\tau}$) and maximal concentrations (C_{max}) were ~5% and 4% lower in Asian, and ~11% and 1% higher in African American than in Caucasian White. Race and ethnicity did not have a clinically meaningful effect on the pharmacokinetics of apremilast.

Hepatic Insufficiency

Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. The AUC_{0-inf} and C_{max} decreased by 5.4% and 15.9% in moderate hepatic impaired subjects and by 1.6% and 35% in severely hepatic impaired patients with wider confidence intervals in the geometric mean ratios, and are not considered clinically meaningful (see **DOSAGE AND ADMINISTRATION).**

Renal Insufficiency

In 8 subjects with mild renal impairment administered a single dose of 30 mg apremilast, the AUC_{0-inf} decreased by approximately 14% and C_{max} increased by approximately 6%. For moderate renally impaired subjects the AUC_{0-inf} increased by approximately 23% and C_{max} decreased by approximately 13%. These changes in AUC_{0-inf} and C_{max} are not considered clinically meaningful (see **DOSAGE AND ADMINISTRATION**).

In 8 subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC_{0-inf} and C_{max} of apremilast increased by approximately 88% and 42%, respectively. These changes in AUC_{0-inf} and C_{max} are considered clinically meaningful (see **WARNINGS AND PRECAUTIONS**, **DOSAGE and ADMINISTRATION).**

Genetic polymorphism

No studies have been conducted specifically to evaluate genetic polymorphisms.

STORAGE AND STABILITY

Store at 15°C - 30°C. Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each diamond-shaped, film-coated tablet contains apremilast, and the following inactive ingredients: microcrystalline cellulose, Anhydrous Lactose, croscarmellose sodium, magnesium stearate, HPMC/ hypromellose, lactose monohydrate, titanium dioxide, triacetin, iron oxide red, iron oxide yellow (for 20 mg and 30 mg), ferrosoferric oxide/black iron oxide (for 30mg).

Tablets are supplied in the following strengths and package configurations:

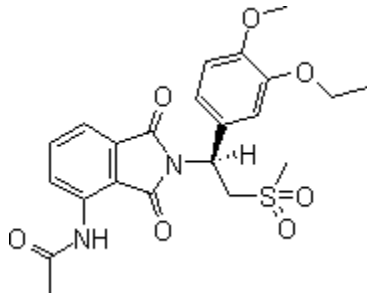
Package configuration	Tablet strength	Description
Bottles of 60 (HDPE bottles with an induction seal and child-resistant cap)	30 mg	The 30 mg tablet beige colored, diamond shape, film coated tablets, debossed with HP on one side and 586 on other side.
28-Count Blister Pack (PVC/aluminum foil blisters)	2 – 30 mg blister cards containing (14) 30 mg tablets	The 30 mg tablet is beige colored, diamond shape, film coated tablets, debossed with HP on one side and 586 on other side.
56-Count Blister Pack (PVC/aluminum foil blisters)	4 - 30 mg blister cards containing (14) 30 mg tablets	The 30 mg tablet is beige colored, diamond shape, film coated tablets, debossed with HP on one side and 586 on other side.
27-Count Starter Pack (PVC/aluminum foil blisters)	Titration portion contains 13 tablets: (4) 10 mg tablets, (4) 20 mg tablets, (5) 30 mg tablets for upward dose titration, with an additional (14) 30 mg tablets for one week of dosing with 30 mg twice daily.	The 10 mg tablet is pink colored, diamond shape, film coated tablets, debossed with HP on one side and 584 on other side. The 20 mg tablet is brown colored, diamond shape, film coated tablets, debossed with HP on one side and 585 on other side. The 30 mg tablet is beige colored, diamond shape, film coated tablets, debossed with HP on one side and 586 on other side.

Legend: HDPE = High density polyethylene; PVC = Polyvinyl Chloride

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Apremilast
Chemical name:	N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide
Molecular formula and molecular mass:	$C_{22}H_{24}N_2O_7S$ 460.5 g / mol
Structural formula:	
Physicochemical properties:	Apremilast is a white to pale yellow non-hygroscopic powder with a melting point of approximately 154°C. It is practically insoluble in water and soluble in acetone.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDY

A double-blind, balanced, randomized, single-dose, two-treatment, two sequence, two-period, two-way crossover, oral bioequivalence study of Apremilast Tablets 30 mg of Marcan Pharmaceuticals Inc., and Otezla® (apremilast) Tablets 30 mg of Celgene Inc., was conducted in 42 healthy, adult, human subjects under fasting condition. A summary of the comparative bioavailability data from the 41 subjects who completed the study is presented in following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Apremilast (1 x 30 mg) Geometric Mean Arithmetic Mean (%CV)				
Pharmacokinetic Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (hr*ng/mL)	2502.77 2660.58 (33.92)	2645.53 2834.09 (38.22)	94.6	91.1 - 98.3
AUC_I (hr*ng/mL)	2606.87 2762.98 (33.23)	2736.85 2926.49 (37.78)	95.3	91.8 - 98.9
C_{max} (ng/mL)	274.52 283.27 (24.53)	339.96 350.65 (24.44)	80.8	76.7 - 85.2
[3]T_{max} (hr)	3.250 (0.75 - 5.00)	2.750 (0.75 - 5.00)		
[4]$T_{½}$ (hr)	6.99 (25.37)	6.47 (24.78)		

[1]Apremilast Tablets 30 mg of Marcan Pharmaceuticals Inc., Canada
[2]Otezla® (apremilast) Tablets 30 mg of Celgene Inc., Canada
[3]Expressed as the median (range) only
[4]Expressed as the Arithmetic mean (%CV) only

Plaque Psoriasis

Study demographics and trial design

Two multicenter, randomized, double-blind, placebo-controlled studies (Studies ESTEEM 1 and ESTEEM 2) enrolled a total of 1257 patients 18 years of age and older , with a diagnosis of plaque psoriasis for at least 12 months, moderate to severe plaque psoriasis at screening [i.e. had a body surface area (BSA) involvement of ≥ 10%, static Physician Global Assessment (sPGA) of ≥ 3 (moderate or severe disease), and a Psoriasis Area and Severity Index (PASI) score ≥ 12], and who were candidates for phototherapy or systemic therapy. Concomitant anti-psoriatic medications were prohibited during the study up to Week 32, with the exception of low potency topical corticosteroids on the face, axillae and groin, coal tar shampoo and/or salicylic acid scalp preparations. Efficacy on a background of other medications or phototherapy has not been adequately studied with apremilast.

Study ESTEEM 1 and Study ESTEEM 2 had a similar design through Week 32. In both studies, patients were randomized 2:1 to Apremilast 30 mg BID or placebo for 16 weeks (Placebo-Controlled Phase). All patients were initiated on study drug with dose-titration over 5 days. From Weeks 16-32, all patients received apremilast 30 mg BID (Maintenance Phase). From Weeks 32-52, a selected subgroup of patients underwent a Randomized Treatment Withdrawal Phase.

In both studies, the primary endpoint was the proportion of patients who achieved PASI-75 at Week 16. The major secondary endpoint was the proportion of patients who achieved a sPGA score of clear (0) or almost clear (1) at Week 16.

Baseline demographics were generally similar across the treatment groups in each study and comparable between the studies. Across both studies, patients ranged in age from 18 to 83 years, with an overall median age of 46 years. A total of 108 patients (8.6%) were aged ≥65 years old, including 9 patients (0.7%) aged ≥75 years old. Most of the patients (68%) were male. Race was predominantly White (90%). Baseline demographics for patients in each trial are presented in Table 6.

Table 6. Summary of Patient Demographics for Studies ESTEEM 1 and ESTEEM 2

Study	Trial design	Dosage, route of administration	Study Subjects (n = number)	Mean age (Range)	Sex
PSOR-008 ESTEEM 1	52-Week, Multicentre, Randomized , Double Blind, Placebo-controlled study	Apremilast 30 mg twice a day PO; placebo	n = 844	46.0 (18, 82)	M = 573 F = 271
PSOR-009 ESTEEM 2	52-Week, Multicentre, Randomized , Double Blind, Placebo-controlled study	Apremilast 30 mg twice a day PO; placebo	n = 411	45.4 (18, 83)	M =276 F = 135

Baseline disease characteristics were generally similar across the treatment groups in each study and comparable between the studies. The mean baseline BSA involvement was 25.19% (median 21.0%), the mean baseline PASI score was 19.07 (median 16.80), and the proportions of patients with sPGA scores of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively. The mean duration since diagnosis of plaque psoriasis was 19 (median 16.6) years. A total of 18% of patients had a history of psoriatic arthritis.

Approximately 35% of patients had not received prior phototherapy, conventional systemic or biologic therapy for the treatment of psoriasis. Approximately 30% of all patients had received prior phototherapy, 38% had received prior conventional systemic therapy, and 30% had received prior biologic therapy for the treatment of psoriasis.

Study results

Clinical Response in Patients with Plaque Psoriasis

The proportion of patients achieving PASI -75 and -50 responses, and a sPGA score of clear (0) or almost clear (1), are presented in Table 7 below. Apremilast resulted in a significant improvement in moderate to severe plaque psoriasis, as demonstrated by the proportion of patients who achieved PASI-75 response at Week 16, compared with placebo. Clinical improvements measured by sPGA and PASI-50 responses were also demonstrated at Week 16 (Table 7).

The proportions of patients who discontinued by Week 16 were 12% in the placebo group and 11% in the apremilast group in ESTEEM 1 and 18% in the placebo group and 13%in the apremilast group in ESTEEM 2.

Table 7. Clinical Response at Week 16[a] in Studies ESTEEM 1 and ESTEEM 2 (FAS[b]; LOCF[c])

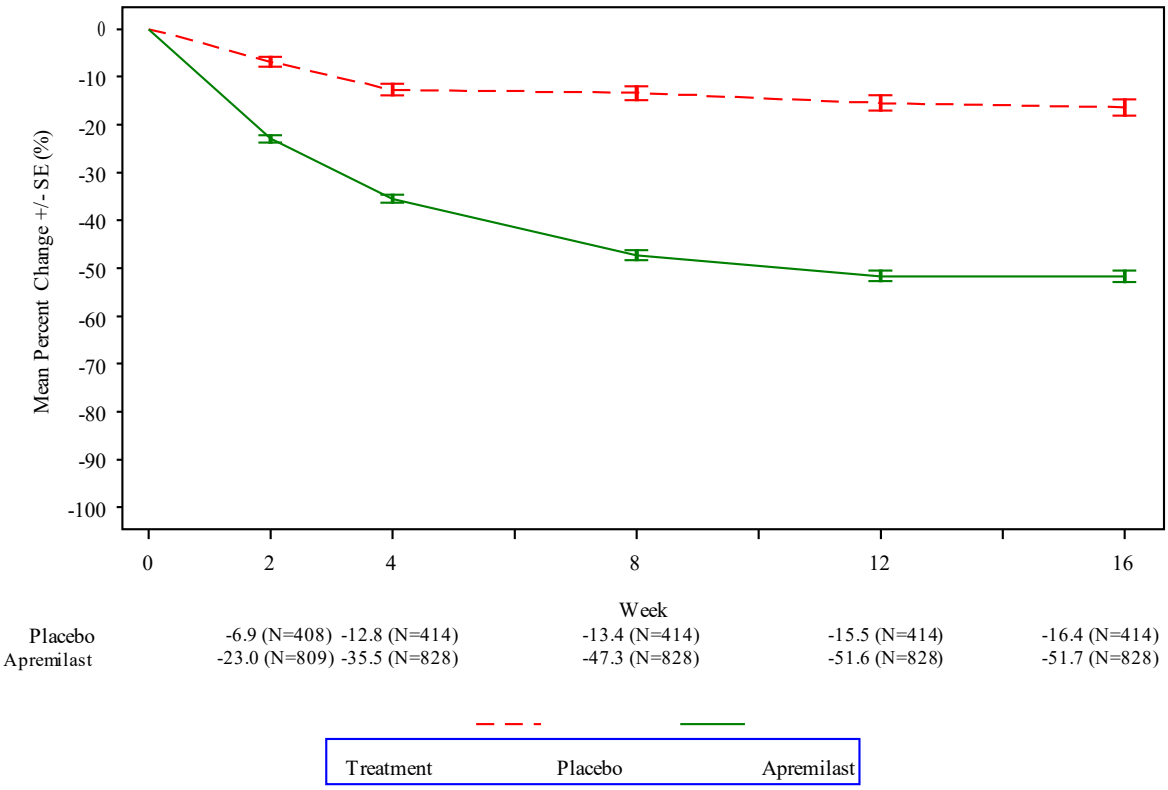
	Study ESTEEM 1		Study ESTEEM 2	
	Placebo	Apremilast 30 mg BID	Placebo	Apremilast 30 mg BID
N	**N = 282**	**N = 562**	**N = 137**	**N = 274**
PASI[d] -75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[e] of Clear or Almost Clear[f], n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)
PASI[d] -50[f], n (%)	48 (17)	330 (58.7)	27 (19.7)	152 (55.5)

[a] All p values < 0.0001
[b] FAS = Full Analysis Set
[c] LOCF = Last Observation Carried Forward
[d] PASI = Psoriasis Area and Severity Index
[e] sPGA = Static Physician Global Assessment
[f] Secondary endpoint

The clinical benefit of apremilast on the primary endpoint (i.e. PASI-75) was demonstrated across subgroups defined by baseline demographics, baseline clinical disease characteristics (including psoriasis disease duration and patients with a history of psoriatic arthritis), prior psoriasis medication usage and response to prior psoriasis treatments. Similar response rates were observed across all weight subgroups, and baseline disease severity classifications including BSA.

Mean percent changes in PASI score from Weeks 0 to 16 are shown in Figure 1..

Figure 1. Studies ESTEEM 1 and ESTEEM 2: Mean Percent Change (Improvement) in PASI Score from Baseline over 16 Weeks ± Standard Error (FAS, LOCF)



Last observation carried forward (LOCF) method was used to impute missing PASI score percent change at each week.

Psoriatic Arthritis

Study demographics and trial design

The safety and efficacy of apremilast was evaluated in 3 multi-center, randomized, double-blind, placebo-controlled trials (Studies PALACE 1, PALACE 2, and PALACE 3) of similar design. A total of 1493 adult patients with active PsA (≥ 3 swollen joints and ≥ 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 PALACE 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), apremilast 20 mg (n = 500), or apremilast 30 mg (n = 497) given orally twice daily. Patients were allowed to receive stable doses of concomitant methotrexate (MTX) (≤ 25 mg/week), sulfasalazine (SSZ) (≤ 2 g/day), leflunomide (LEF) (≤ 20 mg/day), low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone/day), and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the trial. Treatment assignments were stratified based on small-molecule DMARD use at baseline in PALACE 1, 2 and 3.
There was an additional stratification of body surface area (BSA) ≥ 3% with psoriasis in

PALACE 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. At Week 16, patients whose tender and swollen joint counts had not improved by at least 20% were considered non -responders Placebo patients who were considered non-responders were re-randomized 1:1 in a blinded fashion to either apremilast 20 mg twice daily or 30 mg twice daily. Apremilast 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. Baseline demographic characteristics are presented in Table 8. A total of 146 patients (9.8%) were aged ≥65 years old, including 19 patients (1.3%) aged ≥75 years old. Race was predominantly White (94%).

Patients with specific subtypes of PsA were not restricted for enrolment across the 3 studies. The most common subtypes represented in these trials were symmetric polyarthritis (62.0%) and asymmetric oligoarthritis (26.9%). The median duration of PsA disease was 5 years. Prior treatment with small-molecule DMARDs was reported in 76.4% of patients and prior treatment with biologic DMARDs was reported in 22.4% of patients. The majority of patients received concomitant therapy with at least one DMARD, the most common being MTX (54.5%). Apremilast was not studied in combination with biologic DMARDs or with cyclosporine.

Table 8. Summary of Patient Demographics for Studies PALACE 1, PALACE 2, and PALACE 3

Study	Trial design	Dosage, route of administration	Study Subjects (N = number)	Mean age (Range)	Sex
PSA-002 PALACE 1	24-week randomized, double-blind, placebo-controlled phase followed by 28-week, double-blind extension phase	Apremilast 30 mg twice a day PO; Apremilast 20 mg twice a day PO; placebo	N = 504	50.4 (19, 83)	M = 249 F = 255
PSA-003 PALACE 2	24-week randomized, double-blind, placebo-controlled phase followed by 28-week, double-blind extension phase	Apremilast 30 mg twice a day PO; Apremilast 20 mg twice a day PO; placebo	N = 484	50.9 (19, 80)	M = 209 F = 275
PSA-004 PALACE 3	24-week randomized, double-blind, placebo-controlled phase followed by 28-week, double-blind extension phase	Apremilast 30 mg twice a day PO; Apremilast 20 mg twice a day PO; placebo	N = 505	49.7 (18, 77)	M = 236 F = 269

Study results

Clinical Response in patients with psoriatic arthritis

Apremilast resulted in significant improvements in the signs and symptoms of PsA, as assessed by the ACR 20 response criteria, compared to placebo at Week 16. The proportion of patients with ACR 20/50/70 responses in Studies PALACE 1, PALACE 2 and PALACE 3 are shown in Table 9.

Based on data collected up to Week 52, there was no evidence to suggest an attenuation of efficacy on ACR20 for up to 52 weeks of continuous treatment with apremilast.

Table 9. Proportion of Patients with ACR 20/50/70 Responses in Studies PALACE 1, PALACE 2, and PALACE 3 at Week 16

	PALACE 1		PALACE 2		PALACE 3	
Response	Placebo ± DMARDs N = 168	Apremilast 30 mg twice daily ± DMARDs N = 168	Placebo ± DMARDs N = 159	Apremilast 30 mg twice daily ± DMARDs N = 162	Placebo ± DMARDs N = 169	Apremilast 30 mg twice daily ± DMARDs N = 167
ACR 20	19.0%	38.1%*	18.9%	32.1%*	18.3%	40.7%*
ACR 50	6.0%	16.1%	5.0%	10.5%	8.3%	15.0%
ACR 70	1.2%	4.2%	0.6%	1.2%	2.4%	3.6%

* $p \leq 0.01$ for apremilast vs. placebo.
Note: For each study, N is the number of randomized and treated patients for Weeks 16.

Overall, the greater proportions of patients who achieved ACR20 did not appear to be primarily driven by mean improvements on any specific ACR component score(s) (i.e. number of tender joints, number of swollen joints, patient's assessment of pain, patient's global assessment of disease, physician's global assessment of disease, HAQ-DI, and C-reactive protein).

Similar Week 16 ACR20 responses were observed with patients with symmetric polyarthritis and asymmetric oligoarthritis PsA subtypes.

In the pooled post hoc data analyses (Studies PALACE 1, PALACE 2 and PALACE 3), significantly greater ACR 20 responses compared to placebo were observed in both male and female subjects treated with apremilast 30 mg BID. The placebo-adjusted ACR 20 response at Week 16 was higher for male subjects than for female subjects (see **Table 10**).

Table 10. Proportion of Male and Female Subjects Achieving a Modified ACR 20 Response at Week 16 in Pooled Analysis (FAS; NRI)

Sex	Placebo	Apremilast 30 mg twice daily	Treatment effect
Male	16.3%	42.8%	26.5%
Female	21.1%	32.4%	11.6%

FAS = full analysis set; NRI = nonresponder imputation

Physical Function Response

Apremilast-treated patients demonstrated statistically significant improvement in physical function, as assessed by the disability index of the health assessment questionnaire (HAQ-DI) change from baseline, compared to placebo at Week 16. Placebo-adjusted responses on HAQ-DI in patients treated with apremilast 30mg twice daily were -0.182, - 0.140, and -0.127 in PALACE 1, PALACE 2, and PALACE 3, respectively (all significant at $p < 0.01$).

Behçet's Disease

Study demographics and trial design

A multicenter, randomized, placebo-controlled trial (RELIEF) enrolled a total of 207 adult patients with Behçet's disease with active oral ulcers. Patients were previously treated with at least one nonbiologic Behçet's disease medication and were candidates for systemic therapy. Patients met the International Study Group (ISG) Criteria for Behçet's disease. Patients had at least 2 oral ulcers at screening and at least 2 oral ulcers at randomization and without currently active major organ involvement. Concomitant treatment for Behçet's disease was not allowed.

Patients were randomized 1:1 to receive either apremilast 30 mg twice daily (n=104) or placebo (n=103) for 12 weeks (placebo-controlled phase). After Week 12, all patients received apremilast 30 mg twice daily from weeks 12 to 64 (open-label active treatment phase).

Efficacy was assessed based on the number and pain of oral ulcers. The primary endpoint was the area under the curve (AUC) for the number of oral ulcers from baseline through Week 12. Secondary endpoints included other measures of oral ulcers: oral ulcer pain Visual Analog Scale (VAS), proportion of patients achieving resolution of oral ulcers by Week 6, and who remain oral ulcer free at every visit for at least 6 additional weeks, as well as proportion of patients who are oral ulcer-free (complete response) during the 12-week placebo-controlled phase.

Patients ranged in age from 19 to 72, with a mean age of 40 years. The mean duration of Behçet's disease was 6.84 years. All subjects had a history of recurrent oral ulcers that were currently active. The mean baseline oral ulcer counts were 4.2 and 3.9 in the apremilast and placebo groups, respectively.

Study results

Clinical Response in Patients with Behçet's Disease

Apremilast 30 mg twice daily resulted in significant improvement in oral ulcers as demonstrated by the AUC for the number of oral ulcers from baseline through Week 12 ($p<0.0001$), compared with placebo (Table 12). The daily average number of oral ulcers during the 12-week placebo-controlled treatment phase was 2.6 ulcers in the placebo group and 1.5 ulcers in the apremilast 30 mg twice daily group (difference -1.1; 95% CI: -1.6, -0.7).

Table 12. Clinical Response of Oral Ulcers at Week 12 in Study RELIEF (ITT population)

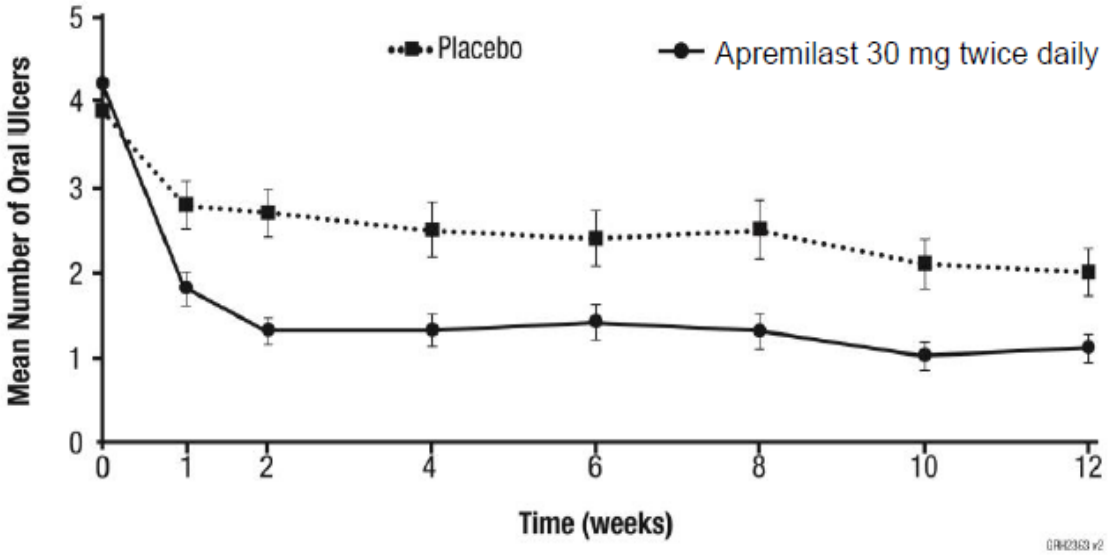
Endpoint	Placebo N = 103	OTEZLA 30 BID N = 104	Absolute Adjusted Treatment Difference[c]
AUC for the number of oral ulcers from baseline through Week 12 (MI)	LS Mean 222.14	LS Mean 129.54	92.60[a]
Change from baseline in the pain of oral ulcers as measured by VAS[b] at Week 12 (MMRM)	LS Mean -18.7	LS Mean - 42.7	24.1[a]
Proportion of subjects achieving resolution of oral ulcers (oral ulcer-free) by Week 6, and who remain oral ulcer free at every visit for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase	4.9%	29.8%	25.1%[a]
Proportion of subjects achieving oral ulcer complete response (oral ulcer-free) at Week 12 (NRI)	22.3%	52.9%	30.6%[a]

ITT=intent to treat; LS=least squares; MI=multiple imputation; MMRM=mixed-effects model for repeated measures; NRI = NRI=non-responder imputation; AUC = area under the curve

[a] p-value < 0.0001 for all Apremilast vs. placebo
[b] VAS=visual analog scale; 0=no pain, 100=worst possible pain
[c] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the Cochran-Mantel-Haenszel weights.

Figure 2 displays the mean number of oral ulcers for each treatment group at each visit, while Figure 3 displays mean oral ulcer pain on a visual analog scale for each treatment group at each visit.

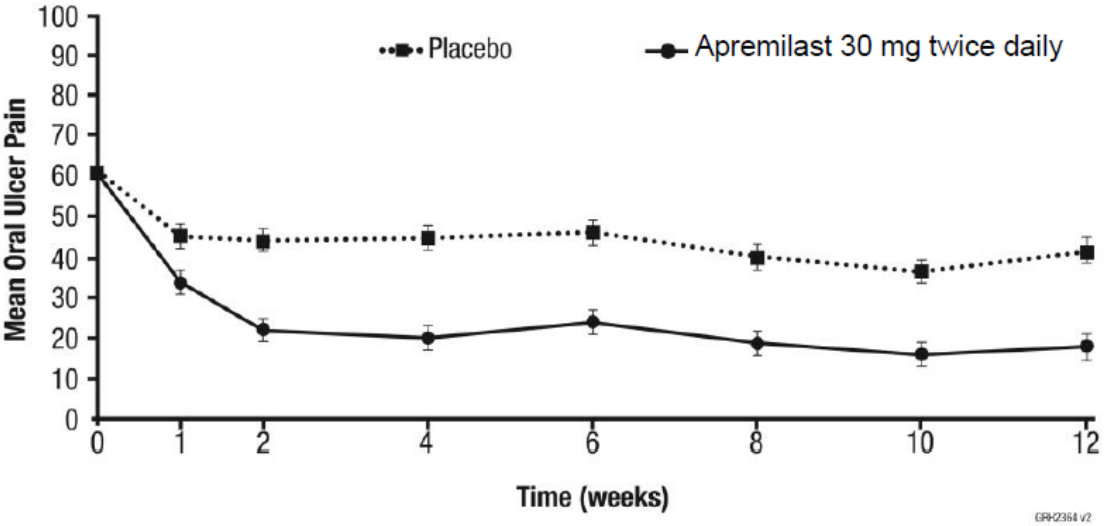
Figure 2. Mean Number of Oral Ulcers by Time Point through Week 12 (ITT Population)



Weeks	0	1	2	4	6	8	10	12
Placebo, n	103	98	97	93	91	86	83	82
Apremilast 30 mg twice daily, n	104	101	101	101	98	94	94	97

ITT = intent-to-treat; SE = standard error.

Figure 3. Mean (± SE) Oral Ulcer Pain on a Visual Analog Scale by Time Point through Week 12 (ITT Population)



Weeks	0	1	2	4	6	8	10	12
Placebo, n	101	95	96	91	90	85	82	81
Apremilast 30 mg twice daily, n	102	95	97	99	97	92	93	95

ITT = intent-to-treat; SE = standard error.
Oral ulcer pain was assessed on a 100-mm Visual Analog Scale with 0 = no pain and 100 = worst possible pain. Mean baseline Visual Analog Scale pain scores were 61.2 and 60.8 in the Apremilast 30 mg twice daily treatment group and placebo treatment group, respectively.

Among 104 patients originally randomized to Apremilast 30 mg twice daily, 75 patients (approximately 72%) remained on treatment and maintained improvements in oral ulcers and reduction of oral ulcer pain through Week 64 (data as observed).

DETAILED PHARMACOLOGY

Animal Pharmacology

Apremilast is a selective small-molecule inhibitor of phosphodiesterase (PDE) 4, which is the dominant PDE in inflammatory cells. PDE4 functions to terminate the action of cyclic AMP (cAMP); an intracellular second messenger that maintains immune homeostasis by suppressing the release of pro-inflammatory mediators and promoting the release of anti-inflammatory mediators.

Phosphodiesterase 4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF -α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis. In cellular models, apremilast inhibits production of TNF-α in human peripheral blood mononuclear cells, synovial cells, plasmacytoid dendritic cells, epidermal keratinocytes, lamina propria mononuclear cells, and whole blood. Other effects include the inhibition of IFN-γ and IL-23A (IL-23p19) production and the elevation of IL-10 production by mononuclear cells, inhibition of GM-CSF, IFN-γ, TNF-α, IL-5, IL-13 and IL-17 by T cells, and the inhibition of IL-8 production by polymorphonuclear cells. Apremilast also inhibited the formation of osteoclasts, cells that can cause bone resorption.

Apremilast has been tested in animal models of acute, rheumatologic, and dermatologic inflammation. In the mouse and the rat, apremilast reduced acute systemic TNF -α production in a dose-dependent manner. In a mouse arthritis model, apremilast significantly inhibited arthritic activity (paw edema) and reduced the histological evidence of arthritis damage in the joint. In a xenograft mouse model of psoriasis, apremilast reduced the severity and incidence of psoriasiform lesions, reduced epidermal skin thickening and proliferation, and reduced the expression of TNF-α, and other inflammatory markers, on the engrafted skin.

Investigations of secondary pharmacodynamics found that apremilast did not significantly bind to any of the cell surface receptors or inhibit any of the other enzymes tested.

Human Pharmacology

Clinical Pharmacodynamics

In an open-label psoriasis study in 19 patients, apremilast treatment was associated with a decrease in dendritic cells and T cells infiltrating the skin lesions within the epidermis and the dermis, a significant decrease in the ex vivo production of TNF -α by the blood, and a significant decrease in iNOS gene expression in the skin after 29 days.

In a subgroup of 20 patients from an open-label study of apremilast for recalcitrant plaque psoriasis, apremilast decreased lesional skin epidermal thickness, reduced the infiltration of myeloid dendritic cells, T cells, and natural killer cells, and decreased the expression of pro-inflammatory genes, including genes encoding iNOS, IL-12/IL-23p40, IL-23p19, IL-17A, IL-22, and IL-8.

Clinical Pharmacokinetics

Apremilast is well absorbed, with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics are linear, with a dose-proportional increase in systemic exposure and less than dose proportional increase in Cmax between the dose range of 10 to 100 mg daily in healthy volunteers. Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution (Vd) is 87 L, indicative of extravascular distribution. Apremilast is metabolized by both cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half -life of approximately 6-9 hours.

TOXICOLOGY

Acute Toxicity

Apremilast has low potential for acute toxicity. In mice, the minimum lethal oral dose was > 2000 mg/kg, and the minimum lethal intravenous (IV) doses were 120 mg/kg and > 120 mg/kg for males and females, respectively. In rats, the minimum lethal IV dose was > 60 mg/kg and < 75 mg/kg, and the minimum lethal oral doses were 2000 mg/kg and > 300 mg/kg for males and females, respectively.

Repeat-Dose Toxicity

Apremilast was evaluated in a series of repeat-dose oral toxicity studies of up to 6 months duration in mice (dose levels of 10, 100 and 1000 mg/kg/day; equivalent to 0.8-, 3.7- and 10-fold clinical exposure based on AUC), 12 months duration in monkeys (dose levels of 60, 180 and 600 mg/kg/day; equivalent to 2.3 -, 3.2- and 4.8-fold clinical exposure based on AUC) and 90 days duration in rats.

Apremilast-related mortality was observed in mice and rats and was primarily attributed to vascular and/or perivascular inflammation. Dose-related inflammatory responses were predominantly observed in mice and rats and included neutrophilia, lymphopenia, and changes in serum proteins (decreased albumin, increased globulin, and increased hapotoglobin, C-reactive protein [CRP], and/or fibrinogen). These inflammatory responses were associated with arteritis and perivascular inflammation in various tissues and organs (e.g. mesentery, heart, lungs, thymus, liver, skeletal muscle, mammary gland, skin and pancreas) in mice and rats, but not in monkeys, even at higher systemic exposures than those achieved in mice and rats. Complete or partial reversibility of the inflammatory findings in mice and rats was observed. Other target organs of apremilast toxicity include non-adverse centrilobular hepatocellular hypertrophy in the liver (mouse) and variable lymphoid depletion in lymphoid tissues (mouse and rat).

The no observed adverse effect level (NOAEL) for the 6-month mouse and 12-month monkey studies, were 10 and 600 mg/kg/day, respectively.

Based on the finding that apremilast induced inflammation in rodents, an investigative *in vitro* study was conducted. The study demonstrated that apremilast stimulates IL-6 production in rodents, but not in monkeys or humans.

Carcinogenicity Studies

Apremilast is not carcinogenic. Daily oral administration to male and female mice at 100

mg/kg/day for 103 or 99 weeks, respectively, at 300/200 mg/kg/day (lowered to 200 mg/kg/day in Week 73) for 98 or 96 weeks, respectively, at 1000 mg/kg/day to males for 73 weeks (dosing was terminated in Week 73), or at 1000/500 mg/kg/day (lowered to 500 mg/kg/day in Week 73) to females for 102 weeks, followed by necropsy in Weeks 102/103, did not show any evidence of carcinogenicity (up to 8.8-fold clinical exposure based on AUC).

In rats, daily oral administration to males at 3 mg/kg/day for 91 weeks, 10/6 mg/kg/day (lowered to 6 mg/kg/day in Week 66) for 89 weeks, and 20 mg/kg/day for 66 weeks followed by euthanasia in Weeks 95 to 100 did not show any evidence of carcinogenicity (up to 0.08-fold clinical exposure based on AUC). Likewise, daily oral administration to female rats at 0.3, 1, and 3 mg/kg/day until Weeks 103, 101, and 94, respectively, followed by necropsy in Week 104, showed no evidence of carcinogenicity (up to 1.1-fold clinical exposure based on AUC).

Genotoxicity Studies

Apremilast is not genotoxic. Apremilast did not induce mutations in an Ames assay or chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Apremilast was not clastogenic in an in vivo mouse micronucleus assay at doses up to 2000 mg/kg/day.

Male Fertility

In a male mouse fertility study, apremilast at oral dosages of 1, 10, 25, and 50 mg/kg/day produced no effects on male fertility. The NOAEL was greater than 50 mg/kg/day (3-fold clinical exposure based on AUC).

Female Fertility and Embryo-fetal Development

In a combined female mouse fertility and embryo-fetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, altered estrous cycling and increased time to mating was observed from 20 mg/kg/day. Nevertheless, all mice mated and pregnancy rates were unaffected. The no observed effect level (NOEL) for female fertility was 10 mg/kg/day (1-fold clinical exposure based on AUC).

Pregnant female mice exhibited increased absolute and/or relative heart weights from 20 mg/kg/day. Increased numbers of early resorptions and reduced numbers of ossified tarsals were observed at doses ≥ 20 mg/kg/day (2-fold clinical exposure). Reduced fetal weights and retarded ossification of the supraoccipital bone of the skull were observed at 40 and 80 mg/kg/day, doses higher than the currently recommended highest human dose. The maternal and developmental NOEL was 10 mg/kg/day (1.3-fold clinical exposure based on AUC). Developmental malformations were not observed up to the highest dosage of 80 mg/kg/day (4.0-fold clinical exposure). Apremilast crosses the maternal blood-placental barrier in mice. Apremilast was not teratogenic in mice.

In a monkey embryo-fetal developmental toxicity study, oral dosages of 20, 50, 200, and 1000 mg/kg/day resulted in a dose-related increase in prenatal loss (abortions) from 50 mg/kg/day (2-fold clinical exposure). Prenatal loss was not observed at 20 mg/kg/day (1.4-fold clinical exposure). No treatment-related fetal developmental effects or malformations were observed in the monkey up to the highest dosage of 1000 mg/kg/day in the study (3.5-fold clinical exposure based on AUC). Apremilast crosses the blood-placental barrier in monkeys. Apremilast was not teratogenic in monkeys.

Pre- and Post-natal Development

In a pre- and post-natal development study, apremilast was administered orally to pregnant female mice at dosages of 0, 10, 80 and 300 mg/kg/day from GD 6 to Day 20 of lactation. One mortality associated with difficulty in delivering pups was observed at 300 mg/kg/day. Clinical signs of maternal toxicity associated with delivering pups were also observed in one mouse in each of the 80 and 300 mg/kg/day dose groups. Apremilast was detected in the milk of lactating mice. Increased peri- and post-natal pup mortality and reduced pup body weights during the first week of lactation were observed at doses ≥ 80 mg/kg/day (≥ 4.0-fold clinical exposure). Pup mortality and developmental effects observed during the first week of the post-natal period were likely related to the apremilast-related pup toxicity (decreased pup weight and viability) and/or lack of maternal care (higher incidence of no milk in the stomach of pups). There were no apremilast-related effects on duration of pregnancy, number of pregnant mice at the end of the gestation period, number of mice that delivered a litter, or any developmental effects in the pups beyond post-natal day 7 during the remaining pre- and post-weaning periods. The NOEL for maternal toxicity and the F 1 generation was 10 mg/kg/day (1.3-fold clinical exposure based on AUC).

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PART III: CONSUMER INFORMATION

PrMAR-APREMILAST

apremilast tablets

This leaflet is part III of a three-part "Product Monograph" published when MAR-APREMILAST was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MAR-APREMILAST. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MAR-APREMILAST is used in adults to treat:

- moderate to severe plaque psoriasis.
- psoriatic arthritis. For these patients, MAR-APREMILAST will be given alone or in combination with methotrexate. It will be given if you cannot use another type of medicine called 'Disease-Modifying Antirheumatic Drugs' (DMARDs) or if you have tried one of these medicines and it did not work.
- oral ulcers associated with Behçet's disease.

MAR-APREMILAST is not approved for use in combination with any other medicines taken by mouth used to treat psoriasis, biological therapies (such as TNF antagonists and anti-IL-12/23 p40 antibodies) or with phototherapy (light therapy using UV light).

What it does:

MAR-APREMILAST belongs to a class of drugs called phosphodiesterase 4 (PDE4) inhibitors. It contains the active ingredient apremilast which works by reducing the activity of PDE4. This results in less inflammation in the skin and joints.

When it should not be used:

Do not take MAR-APREMILAST if you:

- are allergic to apremilast or to any non-medicinal ingredient in the formulation.
- have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

  because lactose is a non-medicinal ingredient in MAR-APREMILAST.
- are breastfeeding. It is not known if MAR-APREMILAST passes into your breast milk. MAR-APREMILAST should not be used if you are breastfeeding.
- are younger than 18 years old.
- are pregnant or intend to become pregnant. It is not known if MAR-APREMILAST will harm your unborn baby. If you take MAR-APREMILAST while you are pregnant, talk to your doctor about how you can be included in the MAR-APREMILAST Enhanced Surveillance Program for Adverse Pregnancy Outcomes.

What the medicinal ingredient is:

apremilast

What the nonmedicinal ingredients are:

Anhydrous Lactose, croscarmellose sodium, ferrosoferric oxide/black iron oxide (for 30mg), hypromellose, iron oxide yellow (for 20 mg and 30 mg), lactose monohydrate, microcrystalline cellulose, magnesium stearate, HPMC/ titanium dioxide, triacetin, iron oxide red

What dosage forms it comes in:

Tablets: 10 mg, 20 mg and 30 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use MAR-APREMILAST talk to your doctor or pharmacist if you:

- have kidney problems.
- have a history of the heart condition, tachyarrhythmia (fast heartbeat or heart palpitations).
- have heart disease or congestive heart failure.
- have tuberculosis or a viral infection such as viral hepatitis, herpes infection or shingles.
- are using immunosuppressive drugs (such as cyclosporine).
- have a history of depression and/or suicidal thoughts or behaviours.
- have low blood pressure
- have any other medical conditions.
- 65 years of age or older.

MAR-APREMILAST can cause weight loss. Your doctor will need to regularly monitor your weight.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all

the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with MAR-APREMILAST:

- Rifampin, used to treat tuberculosis.
- Medicines used to control seizures such as phenobarbital, carbamazepine and phenytoin.
- Medicines that suppress your immune system such as cyclosporine and tacrolimus.
- Methotrexate to treat your psoriasis
- Biological therapies, such as TNF antagonists and anti-IL-12/23 p40 antibodies.
- The botanical medicine St. John's Wort.

PROPER USE OF THIS MEDICATION

Take MAR-APREMILAST exactly as your healthcare provider tells you to take it. MAR-APREMILAST should be taken by mouth and swallowed whole, with or without food. The tablets should not be crushed, split, or chewed.

Usual adult dose:

The recommended dose is 30 mg twice a day. When you first start taking MAR-APREMILAST, the dose needs to be increased gradually; therefore, you must follow the instructions below.

Dose titration schedule:

Day 1		Day 2		Day 3	
AM		AM	PM	AM	PM
10 mg		10 mg	10 mg	10 mg	20 mg
Day 4		**Day 5**		**Day 6**	
AM	PM	AM	PM	AM	PM
20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Overdose:

If you think you or a person you are caring for, have taken too much MAR-APREMILAST, contact healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of MAR-APREMILAST, take it as soon as you remember. If it is close to the time for your next dose, just skip the missed dose. Take the next dose at your regular time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, MAR-APREMILAST can have side effects. If any of these side effects affect you severely, tell your doctor, nurse or pharmacist:

- diarrhea
- nausea
- vomiting
- headache
- upper respiratory tract infection (e.g. common cold)
- flu (body aches and pains, tiredness, fever)
- decreased appetite
- abdominal discomfort, indigestion
- fatigue, trouble sleeping
- back pain
- joint discomfort or pain
- dizziness.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Migraine	√		
Depression		√	
Weight loss		√	
UNCOMMON			
Palpitations: Fast and/or irregular heartbeat	√		
Allergic reaction: Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Infection of the lungs: Shortness of breath, difficult and painful breathing, cough, wheezing and fever		√	
Gastrointestinal hemorrhage (bleeding in the digestive tract): black, tarry stool; blood coming from the rectum, blood in vomit			√
Severe diarrhea: Loose, watery stool			√
Severe nausea: Feeling the need to throw-up			√
Severe vomiting: Throwing up			√

This is not a complete list of side effects. For any unexpected effects while taking MAR-APREMILAST, contact your doctor or pharmacist.

HOW TO STORE IT

Store MAR-APREMILAST at 15°C to 30°C.

Keep MAR-APREMILAST tablets and all medicines out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about MAR-APREMILAST:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); Marcan Pharmaceuticals Inc.'s website www.marcanpharma.com, or by calling 1-855-627-2261.

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