PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

OTEZLA 10 mg (film-coated tablet)

OTEZLA 20 mg (film-coated tablet)

OTEZLA 30 mg (film-coated tablet)

OTEZLA Starter Pack (film-coated tablet)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each OTEZLA 10 mg tablet contains 10 mg apremilast.

Each OTEZLA 20 mg tablet contains 20 mg apremilast.

Each OTEZLA 30 mg tablet contains 30 mg apremilast.

Each OTEZLA Starter Pack contains 10 mg apremilast, 20 mg apremilast and 30 mg apremilast.

Contains sugar (lactose monohydrate):

Each 10 mg film-coated tablet contains 57 mg of lactose (as lactose monohydrate).

Each 20 mg film-coated tablet contains 114 mg of lactose (as lactose monohydrate).

Each 30 mg film-coated tablet contains 171 mg of lactose (as lactose monohydrate).

For full list of excipients, see section 6.1 List of excipients

3 PHARMACEUTICAL FORM

Pink, diamond-shaped, 10-mg film-coated tablet with “APR” engraved on one side and “10” on the opposite side.

Brown, diamond-shaped, 20-mg film-coated tablet with “APR” engraved on one side and “20” on the opposite side.

Beige, diamond-shaped, 30-mg film-coated tablet with “APR” engraved on one side and “30” on the opposite side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- *Psoriatic arthritis:*

  Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs) is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

- *Psoriasis:*

  Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to or who have a contraindication to or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet A light (PUVA).

4.2 Posology and method of administration

Treatment with Otezla should be initiated by medical practitioners experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis.

Posology

The recommended dose of Otezla is 30 mg twice daily taken orally, approximately 12 hours apart (morning and evening), with no food restrictions. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1: Dose Titration Schedule

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

If patients miss a dose, the next dose should be taken as soon as possible. If it is less than 6 hours to the time for their next dose, the missed dose should not

be taken and the next dose should be taken at the regular time.

Special populations

Elderly population:

No dosage adjustment is necessary for elderly patients. Clinical data in patients of 75 years of age or older are limited. Otezla should be used with caution in patients 65 years of age.

Use in patients with impaired renal function:

Otezla dose should be reduced to 30 mg once daily in patients with severe renal impairment (eGFR <30 ml/min/1,73 or creatinine clearance of less than 30 ml per minute estimated by the Cockroft-Gault equation). 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.

Use in patients with impaired hepatic function:

Dose adjustment is not required in patients with hepatic impairment.

The safety of Otezla was not evaluated in PsA or PSOR patients with hepatic impairment.

Paediatric population

No studies have been conducted in patients < 18 years of age.

Method of administration

For oral use.

Otezla tablets should be swallowed whole, either with or without food.

The tablets should not be crushed, split, or chewed.

4.3 Contraindications

- Otezla is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients.
- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Psychiatric disorders

Otezla is associated with an increased risk of psychiatric disorders such as insomnia and depression. Instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression (see section 4.8 Undesirable effects). The risks and benefits of starting or continuing treatment with Otezla should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. Patients, their caregivers and family members should be instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with Otezla

In controlled clinical trials, instances of suicidal ideation and behaviour have been observed in 0,1 % (2/1668) of subjects while receiving OTEZLA, compared to 0,1 % (1/1411) in placebo treated subjects. In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Diarrhoea, nausea, and vomiting

There have been post-marketing reports of severe diarrhoea, nausea, and vomiting associated with the use of apremilast. Most events occurred within the first few weeks of treatment. In some cases, patients were hospitalised. Patients 65 years of age or older may be at a higher risk of complications. If patients develop severe diarrhoea, nausea, or vomiting, discontinuation of treatment with apremilast may be necessary

Severe renal impairment

Otezla should be dose reduced to 30 mg once daily in patients with severe renal impairment (see sections 4.2 and 5.2).

Underweight patients

Patients who are underweight (BMI < 18) at the start of treatment should have their body weight monitored regularly. In the event of unexplained and clinically significant weight loss, these patients should be evaluated by a medical practitioner and discontinuation of treatment should be considered.

Lactose/fructose warning:

Otezla contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g., total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tachydysrhythmia

There have been uncommon reports of tachydysrhythmia, including atrial fibrillation, in Phase 2/3 studies. The incidence of tachydysrhythmia events was 0,2 % for placebo and 0,6 % for Otezla 30 mg BID patients. Of these, atrial fibrillation had an incidence of 0,1 % for placebo and 0,3% for Otezla patients. Use with caution in patients with a history of tachydysrhythmia or conditions that can be worsened by increases in heart rate (e.g. ischaemic heart disease or congestive heart failure).

4.5 Interaction with other medicines and other forms of Interaction

Co-administration of strong cytochrome P450 3A4 (CYP3A4) enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of Otezla, which may result in a loss of efficacy of Otezla. Therefore, the use of strong CYP3A4 enzyme inducers (e.g., rifampicin, phenobarbital, carbamazepine, phenytoin and St. John’s Wort) with Otezla is not recommended.

Co-administration of Otezla with multiple doses of rifampin resulted in a decrease in apremilast AUC and Cmax by approximately 72 % and 43 %, respectively. Apremilast exposure is decreased when administered concomitantly with strong inducers of

CYP3A4 (e.g., rifampicin) and may result in reduced clinical response.
Ketoconazole co-administration increased mean apremilast AUC0-∞ and C_{max} by approximately 36 % and 5 %, respectively, which is not clinically meaningful.
Otezla can be co-administered with a potent CYP3A4 inhibitor such as ketoconazole.
There was no pharmacokinetic interaction between Otezla and methotrexate in psoriatic arthritis patients. Apremilast can be co-administered with methotrexate.
There was no pharmacokinetic interaction between Otezla and oral contraceptives containing ethinyl estradiol and norgestimate. Otezla can be taken with oral contraceptives without clinically relevant interaction.
In clinical studies, Otezla has been administered concomitantly with topical therapy (including corticosteroids, coal tar shampoo and salicylic acid scalp preparations) and UVB phototherapy.
In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC > 50μM). In vitro, apremilast has little to no inhibitory effect (IC 50 > 10μM) on 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) and is not a substrate for these transporters. Hence, clinically relevant drug-drug interactions are unlikely when apremilast is coadministered with drugs that are substrates or inhibitors of these transporters.

Medicine/Laboratory test interactions:

N/A

Other forms of interaction:

N/A

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Pregnancy should be excluded before treatment with Otezla can be initiated. Women of childbearing potential should use an effective method of contraception to prevent

pregnancy during treatment.

Pregnancy

Otezla is contraindicated during pregnancy. There are limited data about the use of apremilast in pregnant women. Effects of Otezla on pregnancy included embryo foetal loss in mice and monkeys, and reduced foetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure (see section 5.3)

Fertility

No fertility data is available in humans. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels 3-fold clinical exposure and in females at exposure levels 1-fold clinical exposure. For pre-clinical fertility data, see section 5.3.

Breastfeeding

Otezla was detected in milk of lactating mice (see section 5.3). It is not known whether Otezla, or its metabolites, are excreted in human milk. A risk to the breastfed infant cannot be excluded, therefore Otezla should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients on Otezla should be advised not to drive or use machinery until they know how Otezla affects them.

4.8 Undesirable effects

a. Summary of the safety profile

Clinical trial data:

The most commonly reported adverse reactions in Phase 3 clinical studies (Studies PALACE 1, PALACE 2, PALACE3, PALACE 4, ESTEEM 1 and ESTEEM 2) have been

gastrointestinal (GI) disorders including diarrhoea (15,7 %) and nausea (13,9 %). They were mostly mild to moderate in severity, with 0,3 % of patients reporting severe diarrhoea and 0,3 % of patients reporting severe nausea. These gastrointestinal adverse reactions generally occurred within the first 2 weeks of treatment and usually resolve within 4 weeks. The other most commonly reported adverse reactions included upper respiratory tract infections (8,4 %), headache (7,9 %), and tension headache (7,2 %) and are mostly mild to moderate in severity. Overall most adverse reactions were considered to be mild or moderate in severity.

The most common adverse reactions leading to discontinuation were diarrhoea (1,7 %) and nausea (1,5 %)

Hypersensitivity reactions were observed infrequently in Otezla clinical studies.

Tabulated list of adverse reactions:

The adverse reactions observed in patients treated with Otezla are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse drug reactions were determined based on data from the Otezla Phase 3 clinical development programme and post-marketing experience. The frequencies of adverse drug reactions are those reported in the apremilast arms of the four Phase III studies in PsA (n = 1,945) or the two Phase III studies in PSOR (n=1184)

The frequency estimates for adverse reactions are defined as:

Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000), Very rare (< 1/10 000); and Not known (cannot be estimated from available data – spontaneous reports).

Preferred terms are coded using the MedDRA (version 14.0).

Summary of adverse reactions in psoriatic arthritis (PsA) and/or psoriasis (PSOR)

System Organ Class	Frequency	Preferred Term
Infections and infestations	Common	Bronchitis
		Upper respiratory tract infection
		Nasopharyngitis*
Immune System disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite*
Psychiatric disorders	Common	Insomnia
		Depression
	Uncommon	Suicidal ideation and behaviour
Nervous system disorders	Common	Migraine*
		Tension Headache*
		Headache*
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very Common	Diarrhoea
		Nausea
	Common	Vomiting
		Frequent bowel movements
		Upper abdominal pain*
		Gastroesophageal reflux disease
		Dyspepsia
	Uncommon	Gastrointestinal

		haemorrhage
Skin and subcutaneous tissue disorders	Uncommon	Rash Urticaria
	Not known	Angioedema
Musculoskeletal and connective tissue	Common	Back pain*
General disorders and administrative site conditions	Common	Fatigue
Investigations	Uncommon	Weight decrease

*At least one of these adverse reactions was reported as serious

Description of selected adverse reactions

Weight Decrease:

The mean observed weight loss in patients treated for up to 52 weeks with Otezla was 1,99 kg. A total of 14,3 % of patients receiving Otezla had observed weight loss greater than 10 %. None of these patients had overt clinical consequences resulting from weight loss. A total of 0,1 % of patients treated with Otezla discontinued due to adverse reaction of weight decreased**. No patient had overt clinical consequences resulting from weight decrease.**

Please see additional warning in section 4.4 for patients who are underweight at beginning of treatment.

Psychiatric disorders

In clinical studies and post-marketing experience, uncommon cases of suicidal ideation and behaviour were reported, while completed suicide was reported post-marketing. Patients and caregivers should be instructed to notify the prescriber of any suicidal ideation (see section 4.4).

Depression:

During the placebo-controlled period of the phase III clinical trials in psoriasis, 1,2 % (14/1184) of patients treated with Otezla reported depression compared to 0,5 % (2/418) treated with placebo. None of these reports of depression was serious or led to study discontinuation.

During the placebo-controlled period of the phase III clinical trials in psoriatic arthritis, 0,9 % (18/1945) of patients treated with Otezla reported depression/depressed mood compared to 0,7 % (5/671) of patients treated with placebo. Depression/depressed mood was reported as serious in 0,1% (2/1945) of patients treated with Otezla and none of the placebo-treated patients. Three patients (3/1945; 0,2 %) treated with Otezla discontinued the study due to depression or depressed mood.

a. Other special populations

Safety in elderly patients

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

Patients with hepatic impairment

The safety of Otezla was not evaluated in PsA or PSOR patients with hepatic impairment. However, Apremilast pharmacokinetics was characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. The $AUC_{0-\infty}$ and Cmax 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. It was concluded that no dose adjustment is necessary in these patients.

Patients with renal impairment

In the PsA or PSOR clinical studies, the safety profile observed in patients with mild

renal impairment was comparable to patients with normal renal function. The safety of Otezla was not evaluated in PsA or PSOR patients with moderate to severe renal impairment in the clinical studies. Apremilast pharmacokinetics was characterised in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60 - 89, 30 - 59, and less than 30 ml/min/1,73 m^2 respectively (see Section 4.2 for dosing recommendation for subjects with severe renal impairment). Apremilast and M12 exposure increased by ~89 % and ~192 % respectively in subjects with severe renal impairment. Their respective clearance also decreased significantly. A dose reduction of apremilast in subject with severe renal impairment is recommended.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: ***https://www.sahpra.org.za/Publications/Index/8***

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8 Undesirable effects).

Patients should be managed by symptomatic and supportive care should there be an overdose.

Otezla was studied in healthy subjects at a maximum total daily dose of 100 mg (given as 50 mg twice daily) for 4,5 days without evidence of dose limiting toxicities. In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code:

Immunosupressants, selective immunosuppressants, L04AA32

Mechanism of action:

Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 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.

Pharmacodynamic effects:

In clinical studies in patients with psoriatic arthritis, apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. In clinical trials in patients with psoriasis, apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22, and IL-8.

Apremilast administered at doses of up to 50 mg twice daily did not prolong the QT interval in healthy subjects.

5.2 Pharmacokinetic properties

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 in the dose range of 10 to 100 mg daily. Accumulation is minimal when apremilast is administered once daily and approximately 53 % in healthy subjects and 68 %

in patients with psoriasis when administered twice daily. Co-administration with food does not alter the bioavailability; 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:

Apremilast is extensively metabolised by both CYP and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation. Oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Apremilast is the major circulating component following oral administration. Apremilast undergoes extensive metabolism with only 3 % and 7 % of the administered parent drug recovered in urine and faeces, respectively. The major circulating metabolite is the glucuronide conjugate of *O*-demethylated apremilast (M12, inactive). Consistent with apremilast being a substrate of CYP3A4, apremilast exposure is decreased when administered concomitantly with rifampicin, a strong inducer of CYP3A4.

In vitro, apremilast and its major circulating metabolite M12 do not inhibit or induce cytochrome P450 enzymes. Hence, apremilast co-administered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of active substances that are metabolised by CYP enzymes

In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC > 50 µM), however clinically relevant drug interactions mediated via P-gp are not expected to occur

In vitro, apremilast has little to no inhibitory effect (IC 50 > 10 µM) on 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) and is not a substrate for these transporters. Hence, clinically relevant interactions are unlikely when apremilast is co-administered with medicines that are substrates or inhibitors of these transporters.

Elimination:

The plasma clearance of apremilast is on average about 10 l/hr in healthy subjects, with a terminal elimination half-life of approximately 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 faeces, respectively.

Special populations:

Pharmacokinetics in Renal Impairment:

There is no meaningful difference in the pharmacokinetics of apremilast between mild or moderate renal impaired subjects and matched healthy subjects (N=8 each group).

The results support that no dose adjustment is needed in patients with mild and moderate renal impairment. Dose should be reduced to 30 mg once daily in patients with severe renal impairment (eGFR less than 30 ml/min/1,73m^2 or CLcr < 30ml/min).

In 8 subjects with severe renal impairment to whom a single dose of 30 mg apremilast was administered, the AUC and Cmax of apremilast increased by approximately 89% and 42%, respectively.

Pharmacokinetics in Hepatic Impairment:

The pharmacokinetics of apremilast and its major metabolite M12 is not affected by moderate (Child Pugh class B) or severe (Child Pugh class C) hepatic impairment. No dosage adjustment is necessary for patients with hepatic impairment.

Pharmacokinetics in the Elderly:

Apremilast was studied in young and elderly healthy subjects. The exposure in elderly subjects (65-85 years of age) is about 13 % higher in AUC and about 6 % higher in C_{max} for

apremilast than that in young subjects (18-55 years of age). No dosage adjustment is necessary for elderly patients.

Pharmacokinetics in Paediatrics:

No studies have been conducted in patients < 18 years of age.

Pharmacokinetics – Gender:

In a Phase 1 study evaluating the effect of gender on the pharmacokinetics of apremilast, the exposure in females was about 28 % and 31 % higher in AUC_{0-t} and $AUC_{0-\infty}$, respectively, and about 8 % higher in C_{max} than that in male subjects. No dosage adjustment is necessary based on gender.

Other Intrinsic Factors:

The pharmacokinetics in Chinese and Japanese healthy subjects is comparable to that in Caucasian healthy subjects. Pharmacokinetic analyses showed apremilast exposure is also similar among Hispanic Caucasians, non-Hispanic Caucasians, and African Americans. No dose adjustment is necessary based on race and ethnicity.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. There is no evidence of immunotoxic, dermal irritation, or phototoxic potential.

Fertility and early embryonic development

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 no observed adverse effect level (NOAEL) for male fertility was greater than 50 mg/kg/day 3-fold clinical exposure).

In a combined female mouse fertility and embryo-foetal developmental toxicity study with

oral dosages of 10, 20, 40, and 80 mg/kg/day, a prolongation of oestrous cycles and increased time to mating were observed at 20 mg/kg/day and above; despite this, all mice mated and pregnancy rates were unaffected. The no observed effect level (NOEL) for female fertility was 10 mg/kg/day (1.0-fold clinical exposure).

Embryo-foetal development

In a combined female mouse fertility and embryo-foetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, absolute and/or relative heart weights of maternal animals were increased at 20, 40, and 80 mg/kg/day. Increased numbers of early resorptions and reduced numbers of ossified tarsals were observed at 20, 40, and 80 mg/kg/day. Reduced foetal weights and retarded ossification of the supraoccipital bone of the skull were observed at 40 and 80 mg/kg/day. The maternal and developmental NOEL in the mouse was 10 mg/kg/day (1,3-fold clinical exposure).

In a monkey embryo-foetal developmental toxicity study, oral dosages of 20, 50, 200, and 1000 mg/kg/day resulted in a dose-related increase in prenatal loss (abortions) at dosages of 50 mg/kg/day and above; no test article-related effect in prenatal loss was observed at 20 mg/kg/day (1,4-fold clinical exposure).

Pre- and post-natal development

In a pre- and postnatal study, apremilast was administered orally to pregnant female mice at dosages of 10, 80 and 300 mg/kg/day from gestation day (GD) 6 to Day 20 of lactation. Reductions in maternal body weight and weight gain, and one death associated with difficulty in delivering pups were observed at 300 mg/kg/day. Physical signs of maternal toxicity associated with delivering pups were also observed in one mouse at each of 80 and 300 mg/kg/day. Increased peri- and postnatal pup deaths and reduced pup body weights during the first week of lactation were observed at ≥ 80 mg/kg/day (≥ 4,0-fold clinical exposure). 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 postnatal day 7. It is likely that pup developmental effects observed during the first week of the postnatal period were 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). All developmental effects were observed during the first week of the postnatal period; no apremilast-related effects were seen during the remaining pre- and post-weaning periods, including sexual maturation, behavioural, mating, fertility and uterine parameters. The NOEL in the mouse for maternal toxicity and F1 generation was 10 mg/kg/day (1,3-fold clinical AUC).

Carcinogenicity studies

Carcinogenicity studies in mice and rats showed no evidence of carcinogenicity related to treatment with apremilast.

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 2,000 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Magnesium stearate

Tablet coating:

OTEZLA 10 mg tablets contain Opadry II Complete Film Coating System Pink, which contains iron oxide red, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

OTEZLA 20 mg tablets contain Opadry II Complete Film Coating System Brown, which contains iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

OTEZLA 30 mg tablets contain Opadry II Complete Film Coating System Beige, which contains iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

OTEZLA Starter Pack of 27 film-coated tablets contains 4 film-coated tablets of OTEZLA 10 mg, 4 film-coated tablets of OTEZLA 20 mg tablets and 19 film-coated tablets of OTEZLA 30 mg tablets

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package/container.

6.5 Nature and contents of container

Otezla Starter Pack

PVC/ aluminium foil blisters containing 27 film-coated tablets (4 x 10 mg, 4 x 20 mg, 19 x 30 mg).

Otezla 30 mg film-coated tablets

PVC/ aluminium foil blisters containing 14 film-coated tablets, in pack sizes of 56 tablets and 168 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements**.**

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Amgen South Africa (Pty) Ltd.

Building D, Ballyoaks Office Park,

Ballyclare Drive,

Bryanston Ext. 7

Johannesburg

2021

South Africa

8 REGISTRATION NUMBER(S)

Otezla Starter Pack: 56/32/0041

Otezla 10 mg: 51/32/0864

Otezla 20 mg: 51/32/0865

Otezla 30 mg: 51/32/0866

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 June 2019

10 DATE OF REVISION OF TEXT

15 November 2022