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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

APTIKA 10 mg (Film-coated tablet)

APTIKA 20 mg (Film-coated tablet)

APTIKA 30 mg (Film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

APTIKA 10 mg: Each film-coated tablet contains 10 mg of apremilast.

Contains sugar: 87,5 mg of lactose monohydrate per film-coated tablet.

APTIKA 20 mg: Each film-coated tablet contains 20 mg of apremilast.

Contains sugar: 175 mg of lactose monohydrate per film-coated tablet.

APTIKA 30 mg: Each film-coated tablet contains 30 mg of apremilast.

Contains sugar: 262,5 mg of lactose monohydrate per film-coated tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

APTIKA 10 mg: White coloured, round shaped, biconvex film-coated tablet, with bevelled edges, debossed with ‘96’ on one side and ‘G’ on another side.

APTIKA 20 mg: White coloured, round shaped, biconvex film-coated tablet, with bevelled edges, debossed with ‘56’ on one side and ‘G’ on another side.

APTIKA 30 mg: White coloured, round shaped, biconvex film-coated tablet, with bevelled edges, debossed with ‘510’ on one side and ‘G’ on another side.

4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

Psoriatic arthritis:

APTIKA, 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:

APTIKA, 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

Posology:

The recommended initial dosage titration of **APTIKA** from Day 1 to Day 5 is shown in Table 1. Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. No re-titration is required after initial titration. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

Table 1: Dosage Titration Schedule

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

Special populations

Elderly patients: No dose adjustment is required for this patient population (see sections 4.8 and 5.2).

Dosage Adjustment in Patients with Renal Impairment:

No dose adjustment is needed in patients with mild and moderate renal impairment. **APTIKA** dosage should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance

(CLcr) of less than 30 mL per minute estimated by the Cockcroft–Gault equation). For initial dosage titration in this group, it is recommended that **APTIKA** be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped (see *Section 5.2*).

Patients with hepatic impairment:

No dose adjustment is necessary for patients with hepatic impairment (see *section 5.2*). The safety of **APTIKA** was not evaluated in PsA or psoriasis in patients with hepatic impairment.

Paediatric population:

The safety and efficacy of apremilast, as contained in **APTIKA**, in children < 18 years have not been established.

Method of administration:

APTIKA is for oral use and can be administered without regard to meals. Do not crush, split, or chew the tablets.

4.3 Contraindications

- Patients with a known hypersensitivity to apremilast or to any of the excipients in the **APTIKA** formulation (see *section 6.1*).
- Pregnancy (see *section 4.6*).

4.4 Special warnings and precautions for use

Psychiatric disorders

Treatment with **APTIKA** is associated with an increase in occurrences of depression. **APTIKA** is also associated with an increased risk of other psychiatric disorders such as insomnia. Instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression (see *section 4.8*). The risks and benefits of starting or continuing treatment with **APTIKA** should be carefully assessed if patients report previous or existing psychiatric symptoms or if

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concomitant treatment with other medicinal products likely to cause psychiatric events is intended. Patients and caregivers 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 apremilast.

Diarrhoea, Nausea, and Vomiting

There have been post-marketing reports of severe diarrhoea, nausea, and vomiting associated with the use of **APTIKA**. Most events occurred within the first few weeks of treatment. In some cases, patients were hospitalised. Patients aged 65 years or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhoea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhoea or vomiting. Patients who reduced dosage or discontinued **APTIKA** generally improved quickly. Consider **APTIKA** dose reduction or discontinuation if patients develop severe diarrhoea, nausea, or vomiting.

Severe renal impairment

APTIKA 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 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.

Excipients:

APTIKA contains lactose. Patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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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 apremilast, which may result in a loss of efficacy of apremilast. Therefore, the use of strong CYP3A4 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin and St. John's Wort) with **APTIKA** is not recommended. Co-administration of apremilast with multiple doses of rifampicin resulted in a decrease in apremilast area-under-the-concentration time curve (AUC) and maximum serum concentration (C_{max}) 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.

In clinical studies, apremilast has been administered concomitantly with topical therapy (including corticosteroids, coal tar shampoo and salicylic acid scalp preparations) and UVB phototherapy.

There was no clinically meaningful interaction between ketoconazole and apremilast. **APTIKA** can be co-administered with a potent CYP3A4 inhibitor such as ketoconazole.

There was no pharmacokinetic interaction between apremilast and methotrexate in psoriatic arthritis patients. **APTIKA** can be co-administered with methotrexate.

There was no pharmacokinetic interaction between apremilast and oral contraceptives containing ethinyl estradiol and norgestimate. **APTIKA** can be co-administered with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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APTIKA is contraindicated in pregnancy (see *section 4.3*).

Breast-feeding

It is not known whether apremilast or its metabolites are present in human milk. Mothers taking **APTIKA** should not breastfeed their infants (see *section 4.3*).

Fertility

No fertility data is available in humans.

4.7 Effects on ability to drive and use machines

Fatigue has been reported with apremilast, as contained in **APTIKA**. Patients should be advised not to drive or use machines until they know how **APTIKA** affects their ability to do so.

4.8 Undesirable effects

The most frequently reported adverse reactions apremilast clinical trails were gastrointestinal (GI) disorders including diarrhoea nausea and vomiting. Other frequently reported adverse reactions included upper respiratory tract infections, headache, and tension headache and back pain.

Tabulated summary of adverse reactions

The adverse reactions observed in patients treated with apremilast 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.

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

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Frequent	Bronchitis, upper respiratory tract infection, nasopharangitis*
Immune system disorders	Less frequent	Hypersensitivity

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Metabolism and nutrition disorders	Frequent	Decreased appetite
Psychiatric disorders	Frequent	Insomnia, depression
	Less frequent	Suicidal ideation and behaviour
Nervous system disorders	Frequent	Migraine*, tension headache*, headache*
Respiratory, thoracic, and mediastinal disorders	Frequent	Cough
Gastrointestinal disorders	Frequent	Diarrhoea*, nausea*, vomiting*, dyspepsia, frequent bowel movements, upper abdominal pain*, gastroesophageal reflux disease
	Less frequent	Gastrointestinal haemorrhage
Skin and subcutaneous tissue disorders	Less frequent	Rash, urticaria
	Frequency unknown	angioedema
Musculoskeletal and connective tissue disorders	Frequent	Back pain*
General disorders and administration site conditions	Frequent	Fatigue
Investigations	Less frequent	Weight decrease

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

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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In overdose, side effects can be precipitated and/or be of increased severity.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 13.9.1 Preparations for Psoriasis

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.

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

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

Distribution

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

Metabolism

Following oral administration in humans, apremilast is a major circulating component (45 %) followed by inactive metabolite M12 (39 %), a glucuronide conjugate of O-demethylated apremilast. Apremilast is metabolised by both cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. In vitro, CYP metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6.

Elimination

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

Specific Populations

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

Renal Impairment: The pharmacokinetics of apremilast is not affected by mild or moderate renal impairment. In 8 subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC and C_{max} of apremilast increased by approximately 88 % and 42 %, respectively.

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Age: 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 young subjects (18 to 55 years of age).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose Monohydrate

Crospovidone Type A

Magnesium stearate

Corn starch dried

Film-coating material:

Hypromellose

Titanium Dioxide

Polyethylene Glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

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The nature and contents of the container of **APTIKA 10, 20 and 30 mg** is summarised in below table:

Package Configuration	Tablet Strength	Packaging Material
Two-week starter pack	13-tablets blister titration pack containing: (4) 10 mg, (4) 20 mg, and (5) 30 mg tablets with an additional (14) 30 mg	Alu-Alu blister pack and PVC/PVdC/PVC blister pack
28-count carton	Two 30 mg blisters containing (14) 30- mg tablets	Alu-Alu blister pack and PVC/PVdC/PVC blister pack
56-count carton	Four 30 mg blisters containing (14) 30 mg tablets	Alu-Alu blister pack and PVC/PVdC/PVC blister pack
56-count carton	13-tablets blister titration pack containing: (4) 10 mg, (4) 20 mg, and (5) 30 mg tablets with an additional (42) 30 mg tablets	Alu-Alu blister pack and PVC/PVdC/PVC blister pack

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Glenmark Pharmaceuticals South Africa (Pty) Ltd

34 Monte Carlo Crescent,

Block A, First floor,

Kyalami Park, Midrand,

1684

8. REGISTRATION NUMBER(S)

To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

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10. DATE OF REVISION OF TEXT