SCHEDULING STATUS

S5

1. NAME OF MEDICINE:

THRYVE 5, THRYVE 10 and THRYVE 15 (uncoated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

THRYVE 5:

Each tablet contains 5 mg of aripiprazole

THRYVE 10

Each tablet contains 10 mg of aripiprazole

THRYVE 15

Each tablet contains 15 mg of aripiprazole

Contains: Lactose

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Uncoated tablets.

THRYVE 5 mg: Off white to light pink colour, modified rectangular shaped, uncoated mottled tablets debossed with '250' on one side and plain on other side

THRYVE 10 mg: White to off white colour, modified rectangular shaped, uncoated tablets debossed with '252' on one side and plain on other side

THRYVE 15 mg: White to off white colour, round shaped, bevelled edge, uncoated tablets debossed with '253' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Schizophrenia: THRYVE is indicated for the treatment of schizophrenia as well as for the maintenance of clinical improvement in adults.

Bipolar mania: THRYVE is indicated for the treatment of acute manic episodes associated with bipolar I disorder and for prevention of recurrence of

new manic episodes in patients who experienced predominately manic episodes and who responded to **THRYVE** treatment

4.2 Posology and method of administration Schizophrenia:

The recommended starting dose for **THRYVE** is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. **THRYVE** is effective in a dose range of 10 to 30 mg/ day. Enhanced efficacy at doses higher than the recommended daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Bipolar mania:

The recommended starting dose for **THRYVE** is 15 mg administered on a once-a-day schedule without regard to meals as mono- therapy or combination therapy (see section 4.5). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I disorder:

For preventing recurrence of manic episodes in patients who have been receiving aripiprazole, continue therapy at the same dose. Adjustments of daily dose, including dose reduction should be considered on the basis of clinical status. Prevention of depressive episodes using aripiprazole monotherapy has not been established. Supplementary therapy should be considered for the prevention or treatment of episodes, as clinically appropriate.

Concomitant medicines: Dosage adjustment for patients taking THRYVE concomitantly with potent CYP3A4 OR CYP2D6 inhibitors:

When concomitant administration of a potent CYP3A4 or CYP2D6 inhibitor with **THRYVE** occurs, the **THRYVE** dose should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is

withdrawn from the combination therapy, the **THRYVE** dose should then be increased (see section 5.2).

Dosage adjustment for patients taking potent CYP3A4 inducers:

When a potent CYP3A4 inducer is added to **THRYVE** therapy, the **THRYVE** dose should be doubled. Additional dose increases of **THRYVE** should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the **THRYVE** dose should be reduced (see section 5.2).

Special Populations

Hepatic impairment: No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. Furthermore, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Renal impairment: No dosage adjustment is required in patients with renal impairment.

Elderly: The safety and efficacy of **THRYVE** in the treatment of schizophrenia or manic episodes in Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: No dosage adjustment is required for female patients as compared to male patients (see section 5.2***).***

Smoking status: According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Paediatric Population

The safety and efficacy of **THRYVE** in patients under 18 years of age have not been established.

Method of administration

THRYVE tablets are for oral use.

4.3 Contraindications

THRYVE is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients.

Paediatric use:

The safety and efficacy of **THRYVE** in patients under 18 years of age have not been established.

4.4 Special warnings and precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Suicide:

The possibility of a suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany medicine therapy. The smallest dose of tablets consistent with good patient management should be prescribed, in order to reduce the risk of overdose.

Cardiovascular disorders:

THRYVE should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with **THRYVE** and preventive measures undertaken.

QT prolongation

THRYVE should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia:

As the risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment, if signs and symptoms of tardive dyskinesia appear in a patient on **THRYVE**, a dose reduction or medicine discontinuation should be considered. These symptoms can temporally deteriorated or even arise after discontinuation of treatment.

Neuroleptic Malignant syndrome:

This is a potentially fatal symptom complex. The clinical manifestation of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestation of NMS, all antipsychotic medicines, including **THRYVE** must be discontinued.

Seizure:

THRYVE should be used cautiously in patients who have a history of seizure disorder or have conditions associated with seizures.

Pathological Gambling and Other Impulse-Control Disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking **THRYVE**. Other urges reported include increased sexual urges, compulsive spending, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive spending, binge or compulsive eating, or other urges while being treated with **THRYVE**. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some

cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse-control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medicine if a patient develops such urges while taking **THRYVE**

Orthostatic hypotension:

Potentially due to its α1- adrenergic receptor antagonist activity, **THRYVE** may be associated with orthostatic hypotension.

Body temperature regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing **THRYVE** for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia:

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicine use. **THRYVE** and other antipsychotic medicines should be used cautiously in patients at risk of aspiration pneumonia.

Elderly patients with dementia-related psychosis:

Elderly patients with dementia – related psychosis treated with **THRYVE**, are at increased risk of death. Most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature.

Cerebrovascular adverse events (e.g. Stroke, transient ischaemic attack), including fatalities, were reported in elderly patients with dementia-related psychosis associated with Alzheimer's disease.

THRYVE should not be used in the treatment of patients with dementia related psychosis.

Weight gain:

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed

lifestyle, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed **THRYVE**. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials **THRYVE** has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with **THRYVE**. Patients with an established diagnosis of diabetes mellitus who are started on **THRYVE** should be monitored regularly for worsening of glucose control (see section 4.8).

Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with **THRYVE** should be monitored symptoms of hyperglycaemia including polyuria, polyphagia and weakness.

Patients who develop symptoms of hyperglycaemia during treatment with **THRYVE** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **THRYVE** was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Patients with ADHD comorbidity:

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of **THRYVE** and stimulants; therefore, extreme caution should be taken when these medicines are co-administered.

THRYVE contains lactose. Patients with rare hereditary conditions such as galactose intolerance, total lactose deficiency or glucose-galactose mal-absorption should not take **THRYVE**.

4.5 Interaction with other medicines and other forms of interaction

General:

Caution should be used when **THRYVE** is taken in combination with other centrally acting medicines due to the primary CNS effects of **THRYVE**.

Concomitant use of **THRYVE** with alcohol should be avoided. Due to its α1-adrenergic receptor antagonist activity, **THRYVE** has the potential to enhance the effect of certain antihypertensive agents.

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

Valproate and lithium:

When valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations and therefore, no dosage adjustment of **THRYVE** is required when administered concomitantly with valproate or lithium.

***Effect of other medicines on THRYVE*:**

There was no clinically significant effect of the H2 antagonist, famotidine, on the pharmacokinetics of aripiprazole.

THRYVE is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Accordingly, no dosage adjustment is required for smokers.

Quinidine and other CYP2D6 inhibitors

THRYVE dose should be reduced to one-half of its prescribed dose when concomitant administration of **THRYVE** with quinidine occurs,
due to increased plasma exposure (AUC) of aripiprazole. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to

have similar effects and therefore, should be accompanied by similar dose reductions.

Ketoconazole and other CYP3A4 inhibitors

Ketoconazole, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and Cmax extensively. The AUC and Cmax of dehydro-aripiprazole also increased substantially.

In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with **THRYVE**, potential benefits should overweigh the potential risks to the patient.

When concomitant administration of ketoconazole with **THRYVE** occurs, **THRYVE** dose should be reduced to one-half of its prescribed dose. Other potent inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors, may be expected to have similar effects and therefore, should be accompanied by similar dose reductions.

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of **THRYVE** should be increased to the level prior to the initiation of the concomitant therapy.

Carbamazepine and other CYP3A4 inducers

THRYVE dose should be doubled when concomitant administration of **THRYVE** occurs with carbamazepine, due to decreased plasma exposure of aripiprazole. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and therefore, should be accompanied by similar dose increases.

Upon discontinuation of potent CYP3A4 inducers, the dosage of **THRYVE** should be reduced to the recommended dose.

Serotonin syndrome

Cases of serotonin syndrome have been reported in patients taking **THRYVE** and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic medicines, such as SSRI/SNRI, or with medicines that are known to increase **THRYVE** concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of use of **THRYVE** during lactation has not been established. Patients must be advised to notify their doctor if they become pregnant or intend to become pregnant during treatment with **[Product Name]**.

Due to insufficient safety information in humans, and the findings that animal studies could not exclude potential developmental toxicity (see Section 5.3), THRYVE should not be used in pregnancy.

Neonates exposed to antipsychotics (including **THRYVE** during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery.

Breast feeding

Safety of use of **THRYVE** during lactation has not been established. **THRYVE** is excreted in human breast milk.

Fertility

THRYVE did not impair fertility based on data from reproductive toxicity studies.

4.7 Effects on ability to drive and use machines

THRYVE has a minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8). Patients should be cautioned about operating hazardous machinery, including motor vehicles until they are reasonably certain that **THRYVE** does not adversely affect them

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4.8 Undesirable effect

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials were akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole.

Tabulated summary of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "Frequency unknown".

	Frequent	**Less-frequent**	**Frequency unknown**
Blood and lymphatic system disorders			Leukopenia, neutropenia, thrombocytopenia

Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face
			oedema, pruritus, or urticaria)
Endocrine disorders		Hyperprolactinaemia	Diabetic hyperosmolar coma, diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia, anorexia, weight decreased, weight gain

Psychiatric disorders:	Insomnia, anxiety, restlessness	Depression, hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) pathological gambling, impulse-control disorders, binge eating, compulsive shopping, poriomania, aggression, agitation, nervousness
Nervous system disorders:	Headache, dizziness, akathisia, somnolence/	Tardive dyskinesia, dystonia	Neuroleptic Malignant Syndrome (NMS), grand mal convulsion, serotonin
	sedation, tremor, extrapyramidal disorder.		syndrome, speech disorder
Eye disorders:	Blurred vision	Diplopia	

Cardiac disorders:		Tachycardia	Torsades de pointes, QT prolongation, ventricular dysrhythmias, cardiac arrest, bradycardia
Vascular disorders:		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis), hypertension, syncope
Respiratory and thoracic and mediastinal disorders:		Hiccups	Aspiration pneumonia, laryngospasm, oropharyngeal spasm
Gastrointestinal disorders:	Nausea, vomiting, constipation,		Pancreatitis, dysphagia, diarrhoea,

	dyspepsia, salivary hypersecretion		abdominal discomfort, stomach discomfort
Hepatobiliary disorders			Hepatic failure, hepatitis, jaundice, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT) Increased alkaline phosphatase

Skin and subcutaneous tissue disorders:			Rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:			Rhabdomyolysis, myalgia, musculoskeletal stiffness
Renal and urinary disorders:			Urinary incontinence, urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism

General disorders and administrative site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema.
Investigations			Blood glucose increased, glycosylated haemoglobin increased, blood glucose fluctuation, increased creatine phosphokinase.

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://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

The potentially medically important signs and symptoms observed includes lethargy, blood pressure increased, somnolence, tachycardia and vomiting. In addition, reports of accidental overdose with **THRYVE** alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence and transient loss of consciousness.

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicine involvement should be considered. Therefore, cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose of **THRYVE**, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after **THRYVE** may be effective for overdose management.

Haemodialysis is unlikely to be useful in overdose management since **THRYVE** is not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties Pharmacotherapeutic group:

Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action:

Aripiprazole efficacy in schizophrenia is mediated through a combination of partial agonist activity at dopamine D2 and serotonin 5 HT1a receptors and antagonist activity at serotonin 5 HT2 receptors.

Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5 HT1a and 5 HT2a receptors and moderate affinity for dopamine D4, serotonin 5 HT2C and 5HT7, Alpha1 –adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for serotonin reuptake site and no appreciable affinity for muscarinic receptors.

Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hyperactivity. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

5.2 Pharmacokinetic properties

THRYVE activity is primarily due to the parent medicine, aripiprazole. The mean elimination half-life of aripiprazole is about 75 hours. Steady- state concentrations are attained within 14 days of dosing. Aripiprazole accumulation by a factor of 5 is predictable with multiple dosing. At steady state, the pharmacokinetics of aripiprazole is dose proportional. There is minimal diurnal variation in the disposition of aripiprazole and its active metabolite, dehydro- aripiprazole. This predominant metabolite in human plasma dehydro- aripiprazole, has been shown to have similar affinities for D2 receptors as the parent compound.

Absorption:

Aripiprazole is well absorbed after oral administration of **THRYVE**, with peak plasma concentrations occur within 3-5 hours after dosing. The absolute oral bioavailability of the tablet formulation of aripiprazole is 87%. The bioavailability of aripiprazole is not significantly affected by administration with food.

Distribution:

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 L/kg. At therapeutic concentrations, aripiprazole is greater than 99% bound to serum proteins, primarily albumin. Aripiprazole did not alter the pharmacokinetics and pharmacodynamics of highly protein bound warfarin, suggesting that protein displacement of warfarin did not occur.

Biotransformation:

Aripiprazole undergoes minimal pre-systematic metabolism. Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation.

CYP3A4 and CYP2D6 enzyme are responsible for dehydrogenation and hydroxylation of aripiprazole, and N- dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicine moiety in systematic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represented about 39 % of aripiprazole AUC in plasma.

Elimination:

Following a single dose of [^{14}C] –labelled aripiprazole, approximately 27 % and 60 % of administration radioactivity was recovered in the urine and faeces, respectively. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % of the oral dose was recovered unchanged in the faeces. The total body clearance of aripiprazole is 0.7 mL /min/kg, which is primarily hepatic.

Special Populations:

The pharmacokinetics of aripiprazole in special populations are described below.

Hepatic impairment:

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B and C), the AUC of aripiprazole, compared to healthy subjects, increased in mild hepatic impairment and in moderate hepatic impairment and decreased in severe hepatic impairment. None of these differences require dose adjustment.

Renal Impairments:

In patients with severe renal impairment (creatinine clearance < 30 mL/min, C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased, but AUC was lower for aripiprazole and higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1 %. No dosage adjustment is required in patients with renal impairments.

Elderly:

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was lower in elderly (≥ 65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects.

No dosage adjustment is recommended for elderly patients (see section 4.4 on increased mortality in elderly patients with dementia related psychosis).

Gender.

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25 %) between men and women.

No dosage adjustment is recommended based on gender.

Race:

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole.

No dosage adjustment is recommended based on race.

Smoking

Based on studies utilising human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2, and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and non-smokers. No dosage adjustment is recommended based on smoking status.

Paediatric population

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

5.3 Pre-Clinical safety data

Animal studies in rats and rabbits could not exclude potential developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Colloidal silicon dioxide, colourants, corn starch, crospovidone, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose

6.2 Incompatibilities

None

6.3 Shelf life

24 months from manufacturing date.

6.4 Special Precautions for storage

Store at or below 25 °C in original container. Protect from moisture.

Do not remove the tablets from the blister strips until required for use

6.5 Nature and contents of container

THRYVE tablets are available in:

- Aluminium/aluminium blister packs of 30 or 100 tablets packed in a carton

- In packs of 30 or 100 tablets in a white opaque HDPE bottle with a child resistant cap (with silica gel pillow pack and cotton pharmaceutical coil).
- In packs of 30 or 100 tablets in a white opaque HDPE bottle with a screw cap (with silica gel pillow pack and cotton pharmaceutical coil).

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be returned to the pharmacy for destruction or it must be disposed of in accordance with local requirements for medical waste destruction

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) LTD
Crownwood Office Park
100 Northern Parkway
Ormonde
Johannesburg
2091
South Africa

8. REGISTRATION NUMBERS

THRYVE 5: 50/2.6.5/0687
THRYVE 10: 50/2.6.5/0688
THRYVE 15: 50/2.6.5/0689

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 December 2020

10. DATE OF REVISION OF THE TEXT