PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

BUPREMED 5 Transdermal Patch
BUPREMED 10 Transdermal Patch
BUPREMED 20 Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BUPREMED 5 Transdermal Patch contains 5 mg buprenorphine in a medicine-containing matrix that releases a nominal 5 µg of buprenorphine per hour over 7 days.

Each BUPREMED 10 Transdermal Patch contains 10 mg of buprenorphine in a medicine-containing matrix that releases a nominal of 10 µg of buprenorphine per hour over 7 days.

Each BUPREMED 20 Transdermal Patch contains 20 mg of buprenorphine in a medicine-containing matrix that releases a nominal of 20 µg of buprenorphine per hour over 7 days.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Transdermal Patches.
BUPREMED 5 Transdermal Patch: A rectangular patch with rounded edges, a beige coloured backing web imprinted with a blue coloured name and respective strength BUPREMED 5 Transdermal Patch, a transparent adhesive matrix laminated with a central placed transparent matrix and a transparent release liner.
BUPREMED 10 Transdermal Patch: A rectangular patch with rounded edges, a beige coloured backing web imprinted with a blue coloured name and respective strength BUPREMED 10 Transdermal Patch, a transparent adhesive matrix laminated with a central placed transparent matrix and a transparent release liner.
BUPREMED 20 Transdermal Patch: A rectangular patch with rounded edges, a beige coloured backing web imprinted with a blue coloured name and respective strength BUPREMED 20 Transdermal Patch, a transparent adhesive matrix laminated with a central placed transparent matrix and a transparent release liner.

4 CLINICAL PARTICULARS

Therapeutic indications
BUPREMED is indicated for the treatment of chronic musculoskeletal pain of the joints and the lower back when that pain is of moderate to severe intensity sufficient to require an opioid to obtain adequate analgesia.

Posology and method of administration
Posology
BUPREMED should be worn continuously for 7 days.
Patients aged 18 years and over:
The lowest BUPREMED dose available, BUPREMED 5 (5 µg/h) should be used as the initial dose in all patients.
Titration
During initiation, titration, and treatment with BUPREMED, patients may continue their existing NSAID or paracetamol regimen as needed.
The dose of BUPREMED should not be increased at less than 3-day intervals when steady state levels are attained.
Changes in BUPREMED dosage may be individually titrated based on the need for supplemental analgesia and the patient's analgesic response to BUPREMED.
To increase the dose, a larger patch should replace the patch that is currently being worn, or a combination of patches should be applied in different places to achieve the desired dose. It is recommended that no more than two patches be applied at the same time, regardless of patch strength.
Titration should continue every 3 - 7 days until adequate analgesia is achieved.
If adequate pain control cannot be achieved with BUPREMED, therapy with BUPREMED should be discontinued and the patient converted to an appropriate analgesic regimen as determined by a physician.

Special populations
Renal impairment:
No special dose adjustment of buprenorphine is necessary in patients with renal impairment.

Hepatic impairment:
There is no need for dosage adjustment when using BUPREMED in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment may accumulate buprenorphine during BUPREMED treatment. BUPREMED should not be used in such patients (see section 4.3).

Paediatric population
The safety and efficacy of BUPREMED in patients under 18 years of age has not been established.

Method of administration
In order to minimise the potential of skin reactions (see section 4.4) BUPREMED should be applied to non-irritated, intact skin of the upper outer arm, upper chest, upper back or the side of the chest. BUPREMED should be applied to a relatively hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Application sites should be rotated whenever a transdermal patch is replaced or added. Application sites should be re-used at no less than 3-week intervals.
If the application site must be cleaned, it should be done with clear water only. Soaps, alcohol, oils, lotions, or abrasive devices should not be used. The skin must be dry before the transdermal patch is applied.
BUPREMED should be pressed firmly in place at the application site, making sure contact is complete, especially around the edges. If the edges of the begin to peel off, the edges may be taped down with suitable skin tape. If a transdermal patch falls off, a new one should be applied. Bathing, showering, or swimming should not affect the system.
While wearing BUPREMED, patients should be advised to avoid exposing the BUPREMED site to direct external heat sources such as heating pads, electric blankets, heat lamps, hot water bottles, etc., as an increase in absorption of buprenorphine may occur. The effects of the use of BUPREMED in hot tubs and saunas have not been studied.

Application directions
Open the pouch just before applying the patch.
Take off the thin cover sheet.
Attach the patch to the upper arm, upper chest, upper back, or sides of the chest. Press the patch with the hand for approximately 30 seconds and check that it is properly attached.
The patch should not be used if the seal is broken.

Discontinuation:
After removal of BUPREMED, plasma concentrations decrease gradually. This should be considered when therapy with BUPREMED is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of BUPREMED.

Contraindications
BUPREMED is contraindicated in:
- patients with known hypersensitivity to buprenorphine or to any of the excipients;
- patients suffering from delirium tremens;
- patients with severe hepatic impairment;
- patients suffering from myasthenia gravis;
- opioid dependent patients and for narcotic withdrawal treatment;
- conditions in which the respiratory centre and function are severely impaired or may become so;
- patients who are receiving MAO inhibitors or have taken them within the last two weeks.

BUPREMED should not be used in patients with head injury, intracranial lesions or increased intracranial pressure, shock or a reduced level of consciousness of uncertain origin.

Special warnings and precautions for use
BUPREMED should not be used in patients with impaired respiratory function and in patients concurrently receiving monoamine oxidase inhibitors (MAOIs) or who have received MAOIs within the previous two weeks (see sections 4.3 and 4.5).

BUPREMED should be used with particular caution in patients with acute alcohol intoxication, head injury, shock, a reduced level of consciousness of uncertain origin, intracranial lesions or increased intracranial pressure BUPREMED is contraindicated in patients with severe hepatic impairment (see section 4.3).

Severe febrile illness may increase the rate of buprenorphine absorption from BUPREMED.
BUPREMED should be used with caution in patients with constipation.
Caution should be exercised in patients suffering from sleep apnoea.
BUPREMED may lower the seizure threshold in patients with a history of seizure disorder.

Since CYP3A4 inhibitors may increase concentrations of buprenorphine (see Section 4.5), patients already treated with CYP3A4 inhibitors should have their dose of BUPREMED carefully titrated since a reduced dosage might be sufficient in these patients.

BUPREMED is not recommended for analgesia in the immediate post-operative period or in other situations characterised by rapidly varying analgesic requirement.

Respiratory depression
Respiratory depression is the primary risk of opioid excess.
Opioids may cause sleep-related breathing disorders including sleep-related hypoxemia and central sleep apnoea (CSA). CSA risk may be increased in a dose-dependent manner with opioid use in some patients. In patients who present with CSA, consider decreasing the total opioid dosage. Pre-existing sleep apnoea may be made worse with opioids (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

CNS depressants co-administration
Concomitant use of sedative medicines such as benzodiazepines or related medicines and buprenorphine may result in sedation, coma, respiratory depression and death. Therefore, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. The lowest effective dose should be used if a decision is made to prescribe opioids concomitantly with sedative medicines. The duration of treatment should be as short as possible. It is unknown if such severity can be expected from transdermal formulation of buprenorphine.
The patients should be followed closely for signs and symptoms of. It is strongly recommended to inform patients and their caregivers to be aware of the symptoms of sedation and respiratory depression (see section 4.5).

Serotonin syndrome
Concomitant administration of buprenorphine and other serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), MAO inhibitors, tricyclic antidepressants or serotonin norepinephrine re-uptake inhibitors (SNRIs) may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
Symptoms of serotonin syndrome may include neuromuscular abnormalities, mental-status changes, autonomic instability and/or gastrointestinal symptoms.
A dose reduction or discontinuation of therapy should be considered if serotonin syndrome is suspected, depending on the severity of the symptoms.

Medicine dependence, tolerance and potential for abuse
Prolonged use of BUPREMED may lead to medicine dependence (addiction), even at therapeutic doses, for all patients. The risks are increased in individuals with mental health disorder (e.g., major depression) or current or past history of substance misuse disorder (including alcohol misuse).
Monitoring and additional support may be necessary when prescribing for patients at risk of opioid misuse.
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained online, and past and present medical and psychiatric conditions.
The risks of developing tolerance should be explained to the patient. The signs that the patient is developing tolerance is that they may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers.
Overuse or misuse may result in overdose and/or death. The clinical need for analgesic treatment should be regularly reviewed. Patients should be closely monitored for signs of misuse, abuse, or addiction.
Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously abused buprenorphine, usually concomitantly with benzodiazepines. Additional overdose deaths due to benzodiazepines and ethanol in combination with buprenorphine have been reported (see section 4.5).
Caution should be exercised when prescribing BUPREMED to patients known to have, or suspected to having, problems with drug or alcohol abuse or serious mental illness.

Medicine withdrawal syndrome
Medicine withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with BUPREMED.
When therapy is no longer required, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.
If withdrawal syndrome occurs, it is generally mild. It begins after 2 days and may last up to 2 weeks. The opioid drug withdrawal syndrome is characterised by some or all of the following: lacrimation, rhinorrhoea, yawning, restlessness, perspiration, chills, mydriasis, myalgia and palpitations. Other symptoms may also develop including agitation, anxiety, hyperkinesia, insomnia, irritability, tremor, weakness, abdominal cramps, nausea, vomiting, diarrhoea, anorexia, increased blood pressure, increased respiratory rate or heart rate.
If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
If the patient on long-term opioid therapy presents with increased pain, hyperalgesia may be diagnosed. This might be qualitatively and anatomically separate from pain related to disease progression or to breakthrough pain stemming from development of opioid tolerance. Pain associated with hyperalgesia tends to be more dispersed than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose. BUPREMED should not be used at higher doses than recommended.

Skin reactions at application site
It is important to follow the posology instructions, to minimise the risk of occurrence of application site skin reactions, (see section 4.2).
Application site reactions with BUPREMED are usually presented by a mild or moderate skin inflammation (contact dermatitis), and their typical appearance may include oedema, pruritus erythema, rash, small blisters (vesicles), and painful/burning sensation at the site of application. Most commonly the cause is skin irritation (irritant contact dermatitis), and these reactions resolve spontaneously after BUPREMED removal. BUPREMED may also cause skin sensitisation and subsequent allergic contact dermatitis (immune mediated, type IV hypersensitivity reaction). Allergic contact dermatitis may develop with a significant delay so it may take months after BUPREMED treatment initiation. It could progress with symptoms similar to irritant contact dermatitis, or with more intense symptoms, such as "burn"-like lesions with discharge and bullae. This may spread outside the application site and may not resolve rapidly after BUPREMED removal. Patients and caregivers should be instructed to monitor the application sites for reactions. If allergic contact dermatitis is suspected, relevant diagnostic procedures should be performed to determine if sensitisation has occurred and its actual cause (buprenorphine and/or other ingredients of the patch). If allergic contact dermatitis has been confirmed, treatment should be discontinued (see section 4.3). Continued BUPREMED treatment in individuals experiencing allergic contact dermatitis may lead to complications, including open wound, bleeding, blistering of the skin, ulceration, and subsequent infections. Mechanical injuries during patch removal (e.g., laceration) are also probable in patients with fragile skin. Chronic inflammation may lead to long-lasting sequelae, such as post inflammatory hyper- and hypopigmentation, as well as thick and dry scaly skin lesions, which can closely resemble scars.

Endocrine system
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include decreases in plasma cortisol and testosterone and an increase in serum prolactin. Clinical symptoms may be evident from these hormonal changes.
BUPREMED is not recommended for analgesia in the immediate post-operative period or in other circumstances described by rapidly varying analgesic requirement.
BUPREMED produces morphine-like effects, including physical dependence and euphoria.
Administration of BUPREMED to persons who are physically dependent on full µ-opioid agonists may precipitate an abstinence syndrome.
BUPREMED may impair the ability to drive and operate machinery.
BUPREMED should not be used at higher doses than recommended.

Interaction with other medicines and other forms of interaction
BUPREMED must not be used concomitantly with MAOIs or in patients who have received MAOIs within the previous two weeks (see sections 4.3 and 4.4).

BUPREMED should be used with caution in patients who are concurrently taking other central nervous system (CNS) depressants or other medicines that may cause hypotension, respiratory depression, profound sedation or potentially result in coma and death. Such medicines include other opioid analgesics, sedatives or hypnotics, general anaesthetics, phenothiazines, alcohol, centrally acting anti-emetics and benzodiazepines.

Buprenorphine should be used cautiously when co-administered with serotonergic medicinal products, such as SSRIs, SNRIs, MAOIs or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Effect of other active substance on the pharmacokinetics of buprenorphine:
Reduction in hepatic blood flow induced by some general anaesthetics (e.g., halothane) and other medicines may result in a decreased rate of hepatic elimination of the medicine buprenorphine.

Buprenorphine as in BUPREMED is mainly metabolised by glucuronidation and to a lesser extent (about 30 %) by CYP3A4. Concomitant treatment with CYP3A4 inhibitors may lead to increased plasma concentrations with exaggerated efficacy of buprenorphine.

Interaction with the CYP3A4 inhibitor ketoconazole will have no clinically relevant increases in mean maximum ($_{Cmax}$) or total (AUC) buprenorphine exposure following BUPREMED with ketoconazole as compared to BUPREMED alone.

The interaction between CYP3A4 enzyme inducers and buprenorphine has not been studied. Co-administration of buprenorphine and enzyme inducers (e.g., phenobarbital, carbamazepine, phenytoin and rifampin) may lead to increased clearance which might result in reduced efficacy.

Fertility, pregnancy and lactation
Women of childbearing potential /Contraception in males and females
BUPREMED should not be used in women of childbearing potential who are not using effective contraception.
Pregnancy
BUPREMED should not be used during pregnancy. There are no or limited data available for the use of buprenorphine in pregnant woman. It has been shown, towards the end of pregnancy, high doses of buprenorphine may induce respiratory depression in the neonate, even after a brief period of administration.
Prolonged use of BUPREMED during pregnancy, may result in neonatal withdrawal.
Buprenorphine has been shown to cross the placenta in humans.
Buprenorphine has been detected in newborn blood, urine and meconium and also in mother's milk at low concentrations.

Breastfeeding
BUPREMED Transdermal Patch should not be used during lactation.
As buprenorphine is excreted in human milk.

Fertility
No human data on the effect of buprenorphine on fertility are available.

Effects on ability to drive and use machines
BUPREMED Transdermal Patch may impair the ability to drive and use machines. This pertains particularly in the beginning of treatment and in conjunction with other centrally acting substances including alcohol, sedatives, tranquillisers and hypnotics.
In cases where a stable dose is used, a general restriction is not necessary.
For patients who experience and are affected by side effects such as dizziness drowsiness and or blurred vision during treatment initiation or titration to a higher dose should not drive or use machines, for at least 24 hours after the patch has been removed.
BUPREMED Transdermal Patch can also impair cognitive function and can affect a patient's ability to drive safely.

Undesirable effects
The following side effects have been reported during the use of buprenorphine:
The table lists adverse reactions reported from 9 completed studies with buprenorphine. The reactions are listed as MeDRA preferred term by system organ class and absolute frequency.
In general, included adverse events are those with a relation to medicine use, and excluded adverse events are minor events, those that are too imprecise to be meaningful, and events that may be commonly observed in the absence of medicine therapy.
Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Immune system disorders	Less frequent	Anaphylactic reaction, hypersensitivity reaction (including oropharyngeal swelling and swollen tongue).
Metabolism and nutrition disorders	Frequent	Anorexia
	Less frequent	Dehydration*
Psychiatric disorders	Frequent	Confusion, depression*, insomnia, nervousness, anxiety.
	Less frequent	Affect lability, aggression, agitation, depersonalisation, euphoric mood, hallucinations, libido decreased, nightmares, psychotic disorder, restlessness, sleep disorder, medicine dependence.
Nervous system disorders	Frequent	Dizziness, headache*, paraesthesia, somnolence, tremor.
	Less frequent	Balance disorder, concentration impairment, coordination abnormal, dysarthria, dysgeusia, hypoaesthesia, involuntary muscle contractions, memory impairment, migraine, paraesthesia, sedation, seizures, speech disorder, syncope*, tremor, convulsions, hyperalgesia, sleep apnoea syndrome.
Eye disorders	Less frequent	Dry eye, eyelid oedema, miosis, vision blurred, visual disturbance.
Ear and labyrinth disorders	Less frequent	Ear pain, tinnitus, vertigo.
Cardiac disorders	Less frequent	Angina pectoris, palpitations, tachycardia.
Vascular disorders	Frequent	Vasodilatation.
	Less frequent	Flushing, hypertension*, hypotension, orthostatic hypotension.
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea*.
	Less frequent	Asthma aggravated*, cough, hiccups, hyperventilation, hypoxia, respiratory depression, respiratory failure, rhinitis, wheezing.
Gastrointestinal disorders	Frequent	Abdominal pain*, constipation*, diarrhoea, dry mouth, dyspepsia*, nausea*, vomiting*.
	Less frequent	Diverticulitis*, dysphagia, flatulence, ileus.
Hepato-biliary disorders	Less frequent	Biliary colic*.
Skin and subcutaneous tissue disorders	Frequent	Erythema, exanthema, pruritus*, rash*, sweating*.
	Less frequent	Contact dermatitis, dry skin, face oedema, pustules, uritcaria.
Musculoskeletal and connective tissue disorders	Frequent	Muscular weakness.
	Less frequent	Muscle cramp, muscle spasm, myalgia.
Renal and urinary disorders	Less frequent	Urinary incontinence, urinary hesitation, urinary retention.
Reproductive system and breast disorders	Less frequent	Erectile dysfunction, sexual dysfunction.
General disorders and administration site conditions	Frequent	Application site reaction† (including application site erythema, application site oedema, application site pruritus, application site rash) asthenia (including muscle weakness), chest pain, pain, peripheral oedema, tiredness.
	Less frequent	Application site dermatitis**, chest pain, fatigue, influenza like illness, malaise, oedema, pyrexia*, rigors*, drug withdrawal syndrome.
Investigations	Less frequent	Alanine amino-transferase increased, weight decreased.
Injury, poisoning and procedural complications	Less frequent	Accidental injury (including fall).

* At least one serious case
†Includes: application site erythema, application site oedema, application site pruritus, application site rash.
**In some cases, late onset local allergic reactions occurred with marked signs of inflammation. In such cases treatment with BUPREMED should be terminated.

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

Overdose
The manifestations of BUPREMED overdose is an extension of its pharmacological actions. Respiratory depression has been absent in some cases of buprenorphine overdose. Respiratory depression including apnoea may occur in other overdose situations. Additional symptoms include sedation, drowsiness, nausea, vomiting, cardiovascular collapse and marked miosis.
Remove any BUPREMED in contact with the patient's skin and dispose of it properly.
Establish and maintain a clear airway, assist and control respiration as indicated, and maintain adequate body temperature and fluid balance. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.
A specific opioid antagonist such as naloxone may reverse the effects of buprenorphine, although naloxone may be less effective in reversing the effects of buprenorphine than other µ-opioid agonists. Treatment with continuous intravenous naloxone should begin with the usual doses but high doses may be required. Maintenance of adequate ventilation is essential when managing a BUPREMED overdose and more important than specific antidote treatment with a narcotic antagonist such as naloxone.

5 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacological classification: A 2.7 Narcotic analgesics
ATC code: N02 AE01
Buprenorphine is a partial agonist µ-opioid, acting at the mu opioid receptor. It also has antagonistic activity at the kappa-opioid receptor.

Pharmacokinetic properties
Buprenorphine may show signs of enterohepatic circulation.
Each buprenorphine base transdermal patch provides a steady delivery of buprenorphine for up to 7 days. Steady state is achieved during the first application. After removal of buprenorphine base transdermal patch, buprenorphine concentrations decline; decreasing approximately 50 % in 12 hours (range 10 – 24 h).

Absorption
Following the patch application, buprenorphine diffuses from the patch through the skin. The median time for a 10 µg/h patch is approximately 17 hours.
Application site:
The absorption does not vary significantly across the specified application sites (upper outer arm, upper chest, upper back or side of the chest). Mean exposure (AUC) at each of the application sites is within approximately ± 11 % of the mean exposure for the four sites.
Following buprenorphine base transdermal patch application, buprenorphine diffuses from the patch through the skin.
Absorption may vary to some extent depending on the application site. Exposure may also be about 26 % higher when applied to the upper back compared to the side of the chest.
Rotation of application sites is recommended, as application repeatedly to the same site, may lead to double the exposure of buprenorphine. Thus, a new patch should not be applied to the same skin site for 3-4 weeks.
Applying direct heat to the patch application site, may lead to a transient 26 – 55 % increase in blood concentrations. Therefore, the use of hot water bottles, heat pads or electric blankets are not recommended.

Distribution
Buprenorphine is approximately 96 % bound to plasma proteins.

Biotransformation
Buprenorphine metabolism in the skin following buprenorphine base transdermal patch application is negligible. Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites.
Hepatic metabolism, through CYP3A4 and UGT1A1/1A3 enzymes, results in two primary metabolites, norbuprenorphine and buprenorphine 3-O-glucuronied, respectively. Norbuprenorphine is glucuronidated before elimination. Buprenorphine is also eliminated in the faeces, with a total elimination to be approximately 55 l/h.
Norbuprenorphine, is the only known active metabolite of buprenorphine.

6 PHARMACEUTICAL PARTICULARS

List of excipients
Levulinic acid, oleyl oleate, povidone (PVP), polyacrylate (dry solids) and polyethylene terphthalate (PET) and 2-propanol.
For the pressure sensitive adhesive (PSA): Copolymer of 2-ethylhexyl acrylate, butyl acrylate, glacial acrylic acid, vinyl acetate (75:15:5:5) (Acrylate polymer I, DT 387-2054)

Incompatibilities
Not applicable

Shelf life
BUPREMED 5 Transdermal Patch: 18 months
BUPREMED 10 Transdermal Patch: 21 months
BUPREMED 20 Transdermal Patch: 36 months

Special precautions for storage
Do not store above 25 °C.

Nature and contents of container
One transdermal patch packed into a heat sealed child-resistant pouch composed of composite material, paper, PET, PE, aluminium, surlyn.

Two or four individually sealed pouches are packed into one outer carton.

Special precautions for disposal and other handling
No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.
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8 REGISTRATION NUMBER(S)

BUPREMED 5: 54/2.7/0227.224
BUPREMED 10: 54/2.7/0228.225
BUPREMED 20: 54/2.7/0229.226

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 October 2024

10 DATE OF REVISION OF THE TEXT

8 July 2024

TRINITY PHARMA

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