SCHEDULING STATUS: S6

1. NAME OF THE MEDICINE

LIV TRIANGLE KUSH MINTS

Strength: Cannabidiol 1 mg/g; Tetrahydrocannabinol 201 mg/g; Cannabigerol 12 mg/g

Pharmaceutical form: Cannabis flos/flower

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cannabidiol 1 mg/g; Tetrahydrocannabinol 201 mg/g;

Cannabigerol 12 mg/g

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Cannabis flos (dried cannabis plant material)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LIV TRIANGLE KUSH MINTS may have a role in a number of medical conditions who have not responded adequately to other medication and who display clinically significant improvement in symptoms during therapy for chemotherapy-induced nausea and vomiting associated with cancer, cancer pain, neuropathic pain, chronic pain (not of cancer origin), fibromyalgia, refractory paediatric epilepsy called Dravets syndrome, palliative care, spasticity from neurological conditions (multiple sclerosis), appetite loss associated with chronic illness, post-traumatic stress disorder (PTSD); Migraines and anxiety.

4.2 Posology and method of administration

LIV TRIANGLE KUSH MINTS is for inhalation use only.

LIV TRIANGLE KUSH MINTS treatment must be initiated and supervised by a physician with specialist expertise in treating the patient.

Smoking cannabis is not recommended. Please use a suitable herbal vaporiser instead, preferably one with convection “air” heating. Do not smoke or vaporise cannabis in the presence of children.

Patients should be advised that it might take up to 2 weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. However, physicians should consider maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity.

To minimise variability of bioavailability in the individual patient, administration of LIV TRIANGLE KUSH MINTS should be standardised as far as possible in relation to food intake.

In addition, starting or stopping some concomitant medicinal products may require a new dose titration.

Titration period:

A titration period is required to reach optimal dose. The number and timing of inhalations will vary between patients.

Maintenance period:

Following the titration period, patients are advised to maintain the optimum dose achieved. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop.

Review by the physician:

A thorough evaluation of the severity of symptoms and of the response to standard medication should be performed prior to initiation of treatment. LIV TRIANGLE KUSH MINTS is only indicated in patients that have not responded adequately to other medication.

The patient's response to LIV TRIANGLE KUSH MINTS should be reviewed after four weeks of treatment. If a clinically significant improvement in symptoms is not seen during this initial trial of therapy, then treatment should be stopped. The value of long-term treatment should be re-evaluated periodically.

Special populations:

The elderly may be more sensitive to the effects of drugs acting on the CNS. Furthermore, as cannabinoids are lipophilic, they may tend to accumulate to a greater extent in elderly individuals since such individuals are more likely to have an increase in adipose tissue, a decrease in lean body mass and total body water, and an increase in the volume of distribution of lipophilic drugs. Lastly, age-related changes in hepatic function such as a decrease in hepatic blood flow and slower hepatic metabolism can slow the elimination of lipophilic drugs and increase the likelihood of adverse effects.

Patients with significant hepatic or renal impairment:

No data with multiple dosing are available in subjects with hepatic impairment. LIV TRIANGLE KUSH MINTS can be administered to patients with mild hepatic impairment without any dose adjustment. Administration to patients with moderate or severe hepatic impairment is not advised due to the lack of information on the potential for accumulation of THC and CBD with chronic dosing.

There are no studies in patients with impaired renal function. However, in these sub-populations the effects of LIV TRIANGLE KUSH MINTS may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations.

4.3 Contraindications

LIV TRIANGLE KUSH MINTS is contraindicated in patients:

- With hypersensitivity to cannabinoids or to any of the excipients
- With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition.
- Who are breast feeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants).

4.4 Special warnings and precautions for use

Cannabis is one of the most widely abused illicit drugs, and can produce physical and psychological dependence.

The drug has complex effects in the CNS and can cause cognitive and memory impairment, changes in mood, altered perception, and decreased impulse control among many other effects.

Cannabis should not be used if patient:

- is under the age of 18
- is allergic to any cannabinoid
- has serious liver, kidney, heart or lung disease
- has a personal or family history of serious mental disorders such as schizophrenia, psychosis, depression, or bipolar disorder
- is pregnant, are planning to get pregnant, or are breast-feeding
- has a history of alcohol or drug abuse or substance dependence.

Psychosis: Anyone experiencing an acute psychotic reaction to cannabis or cannabinoids should promptly stop taking the drug and seek immediate medical attention.

Mild or moderate dizziness is commonly reported. This most frequently occurs in the first few weeks of treatment.

Alterations in pulse rate and blood pressure have been observed following initial dose introduction so caution during initial dose

titration is essential. Fainting episodes may occur. Use of LIV TRIANGLE KUSH MINTS is not recommended in patients with serious cardiovascular disease.

Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures. Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment. These are likely to be the result of transient CNS effects and are generally mild to moderate in severity and well tolerated. They can be expected to remit on reduction or interruption of LIV TRIANGLE KUSH MINTS medication.

Disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions may occur. In any of these circumstances, LIV TRIANGLE KUSH MINTS should be stopped immediately and the patient monitored until the symptom has completely resolved.

No specific studies have been carried out in patients with significant hepatic or renal impairment.

THC and CBD are metabolised in the liver, and approximately one third of the parent drugs and their metabolites are excreted in the urine (the remainder via the faeces). Several THC metabolites may be psychoactive. Thus, the systemic exposure and the effects of LIV TRIANGLE KUSH MINTS are dependent on both renal and hepatic function and in patients with significant impaired hepatic or renal function; the effects of LIV TRIANGLE KUSH MINTS may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations.

There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the CNS adverse reactions of LIV TRIANGLE KUSH MINTS, particularly in elderly patients, could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation.

Although there is a theoretical risk that there may be an additive effect with muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of falls, this has not been seen in published clinical trials, however, patients should be warned of this possibility.

Women of childbearing potential:

LIV TRIANGLE KUSH MINTS may reduce the effectiveness of hormonal contraceptives. Women of childbearing potential must use highly effective contraception while taking LIV TRIANGLE KUSH MINTS. It is currently unknown whether LIV TRIANGLE KUSH MINTS may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should use an additional method of contraception for the duration of therapy and for three months after discontinuation of therapy.

Patients who have a history of substance abuse, may be more prone to abuse LIV TRIANGLE KUSH MINTS as well.

The abrupt withdrawal of long-term LIV TRIANGLE KUSH MINTS treatment may not result in a consistent pattern or time-profile of withdrawal-type symptoms and the likely consequence will be limited to transient disturbances of sleep, emotion or appetite in some patients. No increase in daily dosage may occur in long-term use, and patient self-reported levels of 'intoxication' may be low. For these reasons, dependence on LIV TRIANGLE KUSH MINTS is unlikely.

Adverse reactions which could be associated with the route of administration of the medicine may be reported. Regular inspection of the lungs is also advised in long-term administration.

Travel:

Patients should be advised that if they travel to another country it may not be legal for them to take this medicine into some countries. They should be encouraged to check the legal status before travelling with LIV TRIANGLE KUSH MINTS.

4.5 Interaction with other medicines and other forms of interaction

Potential for LIV TRIANGLE KUSH MINTS to affect other drugs/medicines:

LIV TRIANGLE KUSH MINTS that contains delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) is found to be a reversible inhibitor of CYP3A4, 1A2, 2B6, 2C9 and 2C19 at concentrations far in excess of those likely to be achieved clinically. In vitro investigations also demonstrated that delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) combination had the potential for time dependent inhibition of CYP3A4 at clinically relevant concentrations. The rate of the inactivation of the CYP3A4 enzyme is expected to be rapid. Co-administration of LIV TRIANGLE KUSH MINTS with other CYP3A4 substrates may result in an increase in plasma concentration of the concomitant drug. A review of the dosing regimen of such medication is advised.

An in vitro, CYP induction study data indicated that plasma concentrations of THC and CBD arising from clinical doses, could be sufficient to cause induction of CYP1A2, 2B6 and CYP3A4 at the mRNA level. Co-administration of LIV TRIANGLE KUSH MINTS with other drugs that are metabolised through these cytochrome P-450 enzymes may accelerate the metabolism and reduce the activity of these other drugs such as coumarins, statins, beta-blockers and corticosteroids. When sensitive CYP substrates are co-administered with LIV TRIANGLE KUSH MINTS, review of their dosing regimen is advised.

UGT enzymes:

Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) combination was found to inhibit the UGT enzymes UGT1A9 and UGT2B7 at concentrations that could be achieved in the clinic. Care should be taken when prescribing LIV TRIANGLE KUSH MINTS with concomitant medications which are solely metabolised by both or either of these UGTs (e.g. Propofol and certain antivirals). Patients with genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution when LIV TRIANGLE KUSH MINTS is co-administered.

Potential for LIV TRIANGLE KUSH MINTS to be affected by other drugs/medicines:

The two main components of LIV TRIANGLE KUSH MINTS, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P-450 enzyme system.

Cytochrome P-450 enzyme inhibition:

Concomitant treatment with the CYP3A4 inhibitor ketoconazole is known to produce an increase in Cmax and AUC of THC (1.2- and 1.8-fold, respectively), its primary metabolite (3- and 3.6-fold, respectively) and of CBD (2- and 2-fold, respectively). Therefore, if concomitant drug treatment with CYP3A4 inhibitors (e.g. itraconazole, ritonavir, clarithromycin) is started or stopped during treatment with LIV TRIANGLE KUSH MINTS, a new dose titration may be required (see section 4.2). Concomitant treatment of LIV TRIANGLE KUSH MINTS with the CYP2C9 inhibitor fluconazole (200 mg capsule) may result in an increase in mean THC Cmax of 22 % and mean AUC of 32 %. The Cmax of CBD may also increase by approximately 40 %. Care should be taken when co-administering LIV TRIANGLE KUSH MINTS with potent CYP2C9 inhibitors as it may lead to an increase in exposure to THC, CBD and their metabolites.

Cytochrome P-450 enzyme induction:

Following treatment with the CYP3A4 inducer rifampicin reductions in Cmax and AUC of THC (40 % and 20 % reduction, respectively), its primary metabolite (8 5% and 87 % reduction, respectively) and CBD (50 % and 60 % reduction, respectively) may be observed. Therefore, concomitant treatment with strong enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) should be avoided whenever possible. If deemed necessary, careful titration is recommended, notably within the two weeks following the stop of the inducer.

General:

Care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects.

LIV TRIANGLE KUSH MINTS may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided whilst using LIV TRIANGLE KUSH MINTS, especially at the beginning of treatment or when changing dose. Patients should be advised that if they do drink alcohol while using LIV TRIANGLE KUSH MINTS the additive CNS effects may impair their ability to drive or use machines, and increase the risk of falls.

Hormonal contraceptives:

LIV TRIANGLE KUSH MINTS may induce drug metabolizing enzymes and transporters.

LIV TRIANGLE KUSH MINTS may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add an additional second barrier method.

4.6 Fertility, pregnancy and lactation

Fertility: There is insufficient experience in humans regarding the effects of LIV TRIANGLE KUSH MINTS on reproduction. Therefore, men and women of child bearing potential should take reliable contraceptive precautions for the duration of therapy and for three months after discontinuation of therapy.

Patients on hormonal contraceptives should be advised to use an additional alternative, non-hormonal/reliable barrier method of birth control during LIV TRIANGLE KUSH MINTS therapy.

Pregnancy: It may be prudent to avoid the use of cannabis during pregnancy as there is evidence of reduced neonatal birthweight and long-term developmental problems in children exposed to cannabis in utero. THC readily crosses into the placenta.

Lactation: Cannabinoids are excreted in human milk and may be absorbed by the nursing baby. Because of potential risks to the child, nursing mothers should not use cannabis.

4.7 Driving and using machines

LIV TRIANGLE KUSH MINTS may produce undesirable effects such as dizziness and somnolence which may impair judgement and performance of skilled tasks. Patients should not drive, operate machinery or engage in any hazardous activity if they are experiencing any significant CNS effects such as dizziness or somnolence.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you

4.8 Undesirable effects

The most common adverse event categories may be: nervous system (20 %), GI (13.4 %), and respiratory disorders (12.6 %) and the rate of nervous system disorders, respiratory disorders, infections, and psychiatric disorders higher.

Somnolence (0.6 %), amnesia (0.5 %), cough (0.5 %), nausea (0.5 %), dizziness (0.4 %), euphoric mood (0.4 %), hyperhidrosis (0.2 %), and paranoia (0.2 %) may be related to treatment with cannabis.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization 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

There has been no documented evidence of death exclusively attributable to cannabis overdose to date, most likely because of the sparse expression of CB1 receptors in the brainstem regions responsible for respiratory and cardiovascular control.

A cannabis and THC overdose can produce dose-dependent unwanted and potentially significant mental and physical effects, typically dizziness, sedation, intoxication (euphoria), cognitive impairment, transient impairment of sensory and perceptual functions, clumsiness, dry mouth, hypotension, or increased heart rate. These adverse effects are generally tolerable in healthy adults and not unlike those seen with other medications. Acute psychological complications (e.g. panic attacks, severe anxiety, psychosis, paranoia, hallucinations, convulsions, hyperemesis etc.) that present to hospital Emergency Departments can be managed with conservative measures, such as reassurance in a quiet environment, and/or administration of benzodiazepines (5 to 10 mg diazepam p.o.) or i.v. fluids, if required.

Individuals experiencing psychotic reactions should stop using cannabis or cannabinoids immediately and seek prompt medical/psychiatric attention.

In unconscious patients with a secure airway, activated charcoal should be instilled (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal 227.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other analgesics and antipyretics

ATC Code: N02BG10

5.1 Pharmacodynamic properties

Mechanism of action:

As part of the human endocannabinoid system (ECS), cannabinoid receptors, CB1 and CB2 receptors are found predominantly at nerve terminals where they have a role in retrograde regulation of synaptic function. THC acts as a partial agonist at both CB1 and CB2 receptors, mimicking the effects of the endocannabinoids, which may modulate the effects of partial agonist at both CB1 and CB2 receptors, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g. reduce effects of excitatory neurotransmitters such as glutamate).

5.2 Pharmacokinetic properties

Absorption:

Both THC and CBD are absorbed fairly rapidly and appear in the plasma within 15 minutes after administration, with a mean Cmax of about 4 ng/mL 45-120 minutes after a single dose administration of a 10,8 mg THC dose.

When THC and CBD is co-administered with food the mean Cmax and AUC for THC were 1,6- and 2,8-fold higher compared with fasting conditions. Corresponding parameters for CBD increased 3,3- and 5,1-fold.

There is a high degree of variability in pharmacokinetic parameters between patients. Following a single dose administration under fasted conditions, the mean plasma level of THC showed a 57,3 % CV for Cmax (range 0,97-9,34ng/mL) and a 58,5 % CV for AUC (range 4,2-30,84 h*ng/mL). Similarly, the % CV for CBD was 64,1 % (range 0,24-2,57ng/mL) and 72,5% (range 2,18-14,85 ng/mL) for the same parameters respectively. After nine consecutive days of dosing the % CV values for the same parameters were 54,2 % (Cmax range = 0,92-6,37) and 37,4 % (AUC0-t = 5,34-15,01 h*ng/mL) for THC and 75,7 % (Cmax range 0,34-3,39 ng/mL) and 46,6 % (AUC0-t = 2,40-13,19 h*ng/mL) for CBD respectively.

There is a high degree of variability in pharmacokinetic parameters within patients following single and repeat dosing. Of 12 subjects who received a single dose, eight had reductions in Cmax after nine

days of multiple dosing, whilst three had increases (1 drop-out). For CBD, seven had reductions in Cmax after multiple dosing, whilst four had increases.

When administered oromucosally, plasma levels of THC and other cannabinoids are lower compared with the levels achieved following inhalation of cannabinoids at a similar dose.

Distribution:

As cannabinoids are highly lipophilic, they are quickly absorbed and distributed into body fat. The resultant concentrations in the blood following oromucosal administration of drops are lower than those obtained by inhaling of the same dose of THC because absorption is slower and redistribution into fatty tissues is rapid. Additionally, some of the THC undergoes hepatic first pass metabolism to 11-OH-THC, the first metabolite of THC which then undergoes further oxidation to 11-nor-9-COOH-THC, the most abundant metabolite of THC, and CBD similarly to 7-OH-CBD. Protein binding of THC is high (~97 %). THC and CBD may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the blood stream, then metabolised and excreted via the urine and faeces.

Metabolism:

THC and CBD are metabolised in the liver. Additionally, some of the THC undergoes hepatic first pass metabolism to 11 OH-THC, the first metabolite of THC, which then undergoes further oxidation to 11-nor-9-COOH-THC, the most abundant metabolite of THC, and CBD similarly to 7-OH-CBD. Human hepatic P450 2C9 isozyme catalyses the formation of 11-OH-THC, the primary metabolite, which is further metabolised by the liver to other compounds including 11-nor-carboxy-Δ9-THC (THC-COOH), the most abundant metabolite in human plasma and urine. The P450-3A subfamily catalyses the formation of other hydroxylated minor metabolites. CBD is extensively metabolised and more than 33 metabolites have been identified in urine. The major metabolic route is hydroxylation and oxidation at C-7 followed by further hydroxylation in the pentyl and propenyl groups. The major oxidized metabolite identified is CBD-7-oic acid containing a hydroxyethyl side chain.

See section 4.5 for information on drug interaction and metabolism by the cytochrome P450 enzyme system.

Transporters:

In vitro, cannabis did not inhibit the following transporters at clinically relevant concentrations:

BCRP, BSEP, OAT1, OAT3 OCT2, MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1, MATE1 and P-glycoprotein.

Elimination:

From clinical studies, a non-compartmental PK analysis shows that the first order terminal elimination half-life from plasma is 1,94, 3,72 and 5,25 hours for THC and 5,28, 6,39 and 9,36 for CBD following the administration of 2, 4 and 8 drops respectively.

From the literature, elimination of oral cannabinoids from plasma is bi-phasic with an initial half-life of approximately four hours, and the terminal elimination half-lives are of the order of 24 to 36 hours or longer. Cannabinoids are distributed throughout the body; they are highly lipid soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life.

In a specific hepatic impairment PK study, a single oromucosal dose of 4 drops (10,8 mg THC and 10 mg CBD) showed no significant difference in THC or CBD clearance between subjects with mild hepatic impairment and healthy controls. However, there was substantially reduced clearance and prolonged elimination half-life in the cohorts o subjects with moderate and severe hepatic impairment.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Reprotoxicity studies showed no adverse effects on either male or female fertility in terms of numbers of animals mating; number of fertile males and females, or on copulation or fertility indices. There was no evidence to suggest any teratogenic activity in either rats or rabbits at dosage levels considerably in excess of likely human maximum dosage levels. However, in a rat pre- and post-natal study, pup survival and nursing behaviour were impaired at doses of 2 and 4 mg/kg/day (12 and 24 mg/m2 respectively). Data from the literature have shown negative effects of THC and/or CBD on sperm number and motility. In studies in animals, as expected, due to the lipophilic nature of cannabinoids, considerable levels of cannabinoids were found in the maternal breast milk. Following repeat dosing, cannabinoids are concentrated in breast milk (40 to 60 times the plasma level). Doses in excess of normal clinical doses may affect growth rates of breast-fed infants.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tetrahydrocannabinol (THC); Cannabidiol (CBD); other minor cannabinoids; and volatile/aromatic compounds known as terpenes. The type and amount of these ingredients may vary depending on the cannabis strain.

There are over 70 different cannabinoids as well as hundreds of other chemicals in cannabis. Many of the chemicals found in tobacco smoke are also found in cannabis smoke, for this reason it is recommended that cannabis is not smoked, but vaporised in a suitable vaporiser. Vaporisers heat the material only enough to vaporise the active ingredients in the botanical resin, but not enough to cause combustion, thereby avoiding the toxic chemicals found in cannabis smoke.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

12 months.

6.4 Special precautions for storage

Store all medicines out of reach of children.

Store upright in its carton at or below 25 °C. Keep away from heat and direct sunlight.

Do not use after the expiry date stated on the label.

Do not use LIV TRIANGLE KUSH MINTS if you notice visible signs of deterioration.

Return all unused medicine to your pharmacist.

6.5 Nature and contents of container

LIV TRIANGLE KUSH MINTS is cannabis flos/flower; packaged in a sealed plastic container.

6.6 Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste. Any unused medicine or medicine past its expiry date, as shown on the dispensing label or packaging, should be returned to the pharmacy.

7. HOLDER OF CERTIFICATE OF REGISTRATION

To be allocated

8. REGISTRATION NUMBER(S)

To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT

January 2023