Physician Leaflet: Axiban

1. NAME OF THE PRODUCT

Axiban Sublingual Drops IMC-Medical Grade Cannabis Oil

Axiban T10/C2	Axiban T15/C3	Axiban T10/C10
Axiban T5/C10	Axiban T3/C15	Axiban T1/C20

2. PHARMACEUTICAL FORM

Axiban contains whole extract of cannabis inflorescence formulated in oil, intended for sublingual administration.

Medical cannabis is used to describe products or extracts that are derived from the cannabis plant, which contains a variety of phytocannabinoids (= plant cannabinoids) and other constituents (e.g., terpenes and flavonoids), which a patient legally takes for a specific medical reason, subsequent to the recommendation of the patient's physician and the authorization of the Israel Ministry of Health

3. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle of Axiban contains 10 grams of a whole extract of medical grade cannabis inflorescence that has been formulated in an oil containing medium chain triglycerides (MCT), intended for sublingual administration. The most prevalent and most studied phytocannabinoids in the cannabis inflorescence are THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol), and these are considered to be the main active ingredients.

Medical grade cannabis must be labelled according to the concentration of THC ["T"] and CBD ["C"] that the product contains. [It is customary to write the % of THC first, followed by the % of CBD.] Products that contain more THC than CBD are considered THC-rich, while products that contain more CBD than THC are considered CBD-rich.

Axiban is available in 6 different concentrations, as follows:

Type of product	Name of product	EP*	% THC/% CBD	Total amount per 10 g bottle, mg THC/mg CBD	Amount per drop mg THC/mg CBD
THC-rich	**T10/C2**	4	10% THC/2% CBD	1000 mg THC/ 200 mg CBD	3 mg THC/0.6 mg CBD
	T15/C3	6	15% THC/3% CBD	1500 mg THC/ 300 mg CBD	4.5 mg THC/0.9 mg CBD
Balanced	**T10/C10**	6.5	10% THC/10% CBD	1000 mg THC/ 1000 mg CBD	3 mg THC/3 mg CBD
CBD-rich	**T5/C10**	5	5% THC/10% CBD	500 mg THC/ 1000 mg CBD	1.5 mg THC/3 mg CBD
	T3/C15	5.5	3% THC/15% CBD	300 mg THC/ 1500 mg CBD	0.9 mg THC/4.5 mg CBD
	T1/C20	7	1% THC/20% CBD	100 mg THC/ 2000 mg CBD	0.3 mg THC/6 mg CBD

*Estimate potency = Potency of the product based on the concentration of THC and CBD.

Each bottle of Axiban contains <1.5% cannabinol (CBN), a metabolite of THC that is a marker for aging of the product.

Different concentrations and ratios of THC and CBD have different clinical effects, and the range/diversity of concentrations and ratios of THC:CBD available for Axiban ensure that an individual patient will find the concentration and ratio that is best suited to treat his/her medical condition.

For the list of excipients, see section 6.1.

The manufacture of IMC-medical grade cannabis is highly regulated and controlled. IMC-medical grade cannabis, like Axiban, is manufactured according to high quality standards and in accordance with IMC-Good Manufacturing Practice, ensuring no contamination, batch-to-batch consistency and quality control.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

The Israel Ministry of Health has outlined in Guidance 106 the 12 indications for which medical cannabis is indicated. According to this guidance, the 11 indications for Axiban are: Chemotherapy-induced nausea and vomiting (CINV) or chemotherapy-induced pain, metastatic cancer pain, inflammatory bowel disease, neuropathic pain, spasticity of multiple sclerosis, pain in Parkinson's disease, cachexia in AIDS, Tourette's syndrome, recalcitrant epilepsy in adults, palliative care for terminally ill patients, and post-traumatic stress disorder. (Note: According to Guidance 106, medical cannabis is also indicated for recalcitrant epilepsy in pediatric patients.) In general, the use of medical cannabis is indicated in patients who have adequately tried and failed conventional therapies. Please refer to Guidance 106 for details on the specific criteria required for initiating medical cannabis and for subsequent continuation, for each of the 12 indications.

In addition, for an individual patient with a clinically significant medical condition that cannot be adequately managed by conventional therapy and which is not included as one of the 12 approved indications (eg autism, fibromyalgia), the physician can appeal to the MOH Committee for Medical Cannabis to ask for approval on an individual, exceptional basis.

4.2 Posology and Method of Administration

<u>Posology</u>

Prior to treatment initiation, physician and patient should agree <u>ahead-of-time</u> on the goals of therapy, taking into account both the symptoms (e.g., reduction of 30% in pain) and function/quality of life (e.g., ability to dress oneself)." Exit strategies", when treatment goals are not met, should also be agreed upon prior to treatment initiation. Furthermore, the physician should assess the patient's risk of addiction or misuse using a set series of questions or a self-questionnaire. Patients who are at risk will need to be monitored more closely. Upon treatment initiation, patients should be given 2 tables to complete, one that tracks intake (product concentration, date, time of intake, number of drops per intake) and one that tracks outcome (efficacy, adverse effects, duration of action), which will function as a guide during the titration process (see below). Patients should be advised that adherence to the dosing regimen over time is essential for optimal efficacy.

The posology should be in accordance with the principles outlined in the IMC-GCP guidance published by the Israel Ministry of Health.

The maximum amount of cannabis allowed when starting therapy is 20 g.

Initial titration

The general principle of dosing is: "Start Low, Go Slow". This is true both for choosing a concentration and also for choosing the dose.

a) Choosing a concentration: Most patients should start on the concentration recommended in the table below, in accordance with the indication for use. All patients should then be gradually titrated upwards to achieve the lowest dose that adequately addresses the patient's symptoms and/or achieves the target goals of therapy, with no or tolerable adverse effects.

THC:CBD ratio	**Indication**
T10/C2	CINV or pain due to chemotherapy, metastatic cancer pain, Parkinson's pain, Tourette's, PTSD
T10/C10	Neuropathic pain, AIDS cachexia, multiple sclerosis spasticity, palliative care (terminal patients), PTSD
T5/C10	IBD
T1/C20	Adults with recalcitrant epilepsy
T0/C24 (Axiban is not available in this dosage)	Pediatric patients with recalcitrant epilepsy

b) Choosing a dose: Patients should begin therapy with 1 drop daily, to be taken preferably at night before bedtime. Thereafter, once every few days, as necessary, the patient can gradually increase the dose little by little, either increasing the number of intakes per day or the number of drops per intake. Each change should be small. As one example, a patient can start with 1 drop nightly, then 1 drop twice daily, followed by three times daily, ultimately aiming to accord with the patient's self-reported duration of action. For example, if a patient reports efficacy for 8 hours, then the medical cannabis should be taken 3 times daily, but if the patient reports efficacy for 4 hours then the medical cannabis should be taken 6 times daily. (Note: Six times daily = 4 hours interval between intakes, is the maximum number of intakes per day.) Patients can also gradually increase the number of drops taken per intake in accordance with the patient's self-reported efficacy. Patients should begin by increasing the number of drops (increasing by 1 drop only) at a single intake only, and thereafter, gradually increase the number of intakes with the new number of drops. The number of drops taken can be asymmetric and in accordance with the patient's symptoms/daily routine. For example, if a patient reports more pain at night, the dose taken during the day can be 2 drops and the dose taken before bedtime can be 3-4 drops. If a patient reports adverse events, such as dizziness, then the next dose should be reduced and once the reduced dose is no longer associated with adverse effects, the titration process can be resumed more gradually, as necessary.

The titration process must be individualized, based on the patient's symptoms and response to the medical cannabis. There is no fixed correlation between dose and weight, nor between dose and severity of symptoms. The 2 tables that the patient must complete regarding intake and outcome will guide the physician during the titration process, whether

and/or how frequently to raise (or lower) the dose. The titration phase can take several weeks or more, and patients should be forewarned that the process is slow and that it may take some time to assess the efficacy and any adverse effects of the medical cannabis.

Changes after initial titration

If after 2 months the patient reports inadequate efficacy despite using the maximum number of drops (about 20 drops daily for a monthly usage of 20 g of Axiban), then the physician can consider one of two options (see Table below):

a) Increasing the amount of Axiban dispensed to the patient (e.g., increase from 20 g/month to 30 g/month). This is represented by downward vertical lines in the table. Any increase in the amount dispensed is limited to 10 g/month and the increase should be done gradually over the course of 2 months.
b) Increasing the concentration of the product (e.g., increase from 10%THC to 15%THC). This is represented by upward diagonal lines in the table. An increase in the THC concentration of the product will require a commensurate reduction in the number of drops per intake in accordance with the reduction in the number of grams per month (for example, the number of drops should be reduced 30% when reducing the number of grams per month from 30 to 20). If patients then need to undergo a further titration, it should be gradual. If the change involves an increase in the CBD concentration and does not involve an increase in the THC concentration (e.g., switch from T10/C2 to T10/C10), then there is no need for a commensurate reduction in the number of drops per intake. Such changes are represented by the horizontal lines in the table.

If the patient cannot find an effective does that does not produce significant adverse effects, switching to a product with a different THC:CBD ratio may be helpful. This is represented by horizontal lines in the table. For example, a patient who continues to complain of euphoria can be switched to a product with a lower THC content and a higher CBD content. After the switch, patients will need to undergo a further titration, which should be gradual. Physicians should take into account that it is also possible for the patient to use 2 products with different THC:CBD ratios, matching the product to their symptoms/daily routine. For example, a patient may report better outcome using a THC-dominant strain during the day and a CBD-dominant strain before bedtime.

CBD Rich								THC Rich							
8		7		5.5		5		4		6.5		6		8	E.P
T0 C24		T1/C20		T3/C15		T5/C10		T10/C2		T10/C10		T15/C3		T20/C4	מוצר הקנביס
20	↔	20	↔	20	↔	20	↔	20	↔	20	→	20	→	20	כמות קנביס לחודש (גרם)
↓	↘	↓	↘	↓	↘	↓		↓	↘	↓	↘	↓	↘	↓	
30	←	30	←	30	←	30	↔	30	→	30		30		30	
↓		↓		↓		↓		↓	↘	↓	↘	↓	↘	↓	
40	←	40	←	40	←	40		40	→	40		40		40	
↓		↓		↓		↓		↓	↘	↓	↘	↓	↘	↓	
50	←	50	←	50	←	50		50	→	50		50		50	
		↓		↓		↓		↓	↘	↓	↘				
*		60	←	60	←	60		60	→	60		*		*	
*		*		*		*		*		*		*		*	

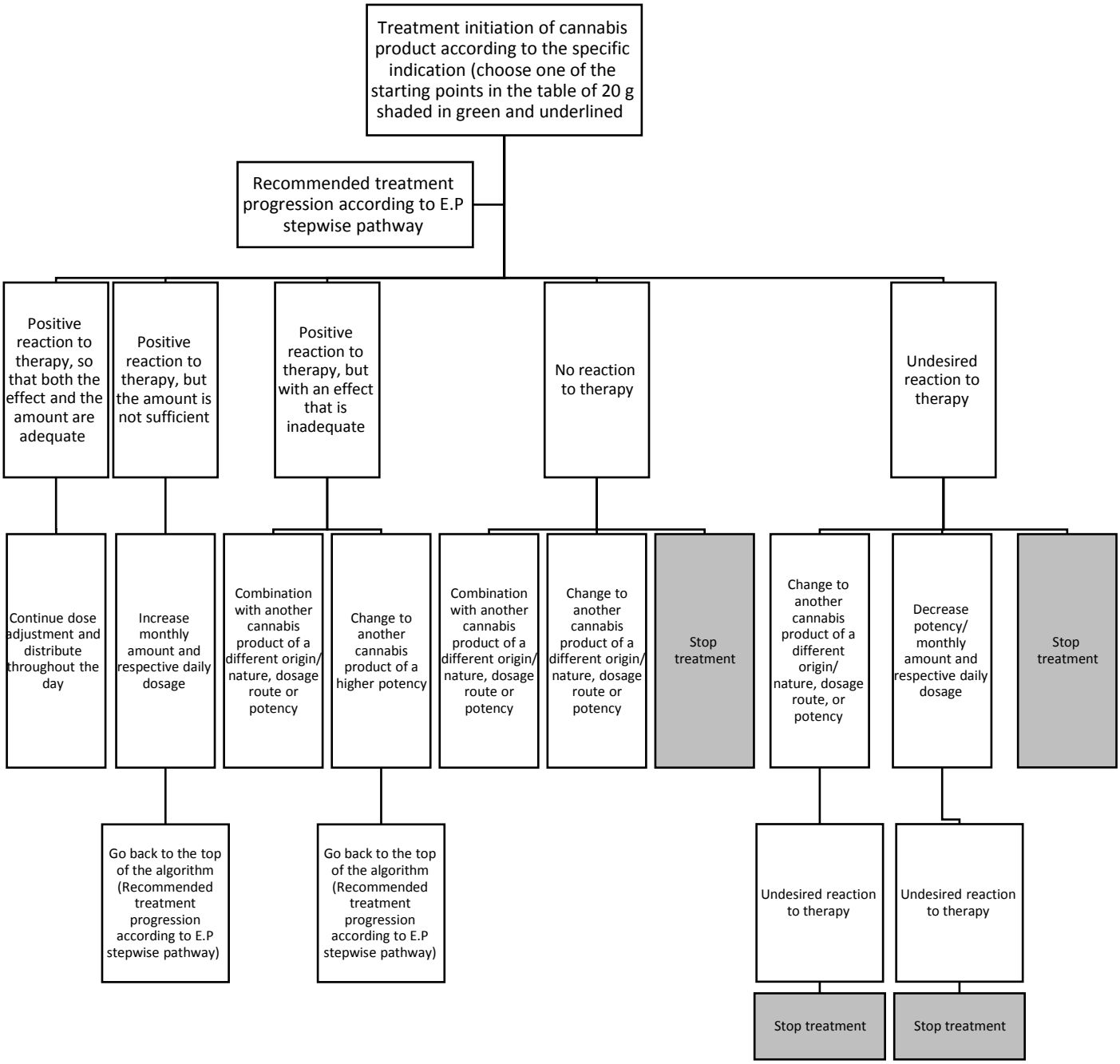
Explanations to Table: The table presents the starting point of therapy and the steps one should follow when making changes. One may start therapy only with underlined products shaded in green. Any changes should follow the direction of the arrows. If a change leads to an unwanted event, one should return to the previous step, or change to a new starting point (shaded in green). The amount of monthly cannabis is the maximum amount noted in the patient's license. An asterisk represents monthly amounts that are not usually recommended, and which require special MOH approval and supporting documentation.

While the above table shows the general progression of steps one should take after the initial titration, a more tailored approach taking into account the specific indication is presented below:

Indication*	Starting Axiban concentration	Axiban concentration for the next step(s)
CINV or pain due to chemotherapy, metastatic cancer pain (except hepatoma), Parkinson's pain, Tourette's syndrome	T10/C2	T10/C10 T15/C3
Neuropathic pain	T10/C10	May combine THC-rich product for fast relief with CBD-rich product for long-lasting relief
Multiple sclerosis spasticity	T10/C10	T10/C2 T15/C3 If necessary, may combine with CBD-rich product
Palliative care AIDS cachexia	T10/C10	T10/C2 T15/C3
IBD	T5/C10	T3/C15 T1/C20
Recalcitrant epilepsy in adults	T1/C20	T0/C24 (Axiban is not available in this concentration) If necessary, may combine with or use T3/C15 or T5/C10
PTSD	T10/C10, or T10/C2	T5/C10 T3/C15 T1/C20 If necessary may combine with THC-rich product for fast relief, at most T15/C3

*For details of the full indication and required preconditions, please consult MOH guidance 106 & IMC-GCP.

Below is a flowchart outlining the treatment protocol as recommended by the MOH.



Changes over time

A patient may require an increase in dose or concentration over time due to a progression of the disease (e.g., cancer pain) or due to the development of tolerance, which can occur with medical cannabis. Regardless of the cause, the patient should be re-titrated to effect. Alternatively, a "drug holiday", during which the patient temporarily stops taking the medical cannabis, may enable the patient to achieve efficacy with a lower dose upon treatment re-initiation. In addition, a patient might over time change concomitant medicines or experience a change in a medical condition other than the cannabis-condition. Such changes may also mandate a change in daily dose, concentration or a switch to another product with a different THC:CBD ratio.

An increase in the amount dispensed per month requires prior approval by the Ministry of Health. Doses higher than 40 gram are considered high doses. Doses above 50-60 gram per month mandate a critical assessment, whether the patient should be switched to a more concentrated product or a product with a different THC:CBD ratio, or whether treatment with medical cannabis should be discontinued if therapeutic targets are not being met. Doses higher than 100 gram per month require special permission from the Ministry of Health and convincing, supportive documentation.

Monitoring patients

During the initial titration phase and upon any change in dosage, patients should be closely monitored for efficacy and adverse effects. Once patients are stabilized on an appropriate dose, the follow up interval can be lengthened. Nevertheless, at all time during treatment with medical cannabis, patients should be periodically followed up to ensure that treatment goals continue to be met and that there are no signs of misuse/addiction.

Discontinuing therapy

If the patient cannot find a particular product that achieves the therapeutic target with minimal or tolerable adverse effects (even after changing the dose or changing to a different THC:CBD ratio), treatment with Axiban should be discontinued. Some patients treated with sublingual medical cannabis may achieve better efficacy with inhaled medical cannabis. In addition, if the patient show signs of misuse or addiction, treatment with medical cannabis should be discontinued and if appropriate, an addiction specialist should be consulted. It is recommended to gradually reduce the dose over time, performing a downward titration process that is the reverse of the upward titration process. If at any time during the process, the patient develops withdrawal symptoms, the dose can be temporarily increased until the patient stabilizes, after which the downward titration can be continued but more gradually. For patients who continue to achieve a favorable risk-benefit ratio with medical cannabis for a chronic condition, there is no maximum duration of therapy.

Method of administration

Axiban is administered as drops sublingually and each bottle contains about 330 drops. Upon treatment initiation, all patients will be supplied with a single month's supply of up to 20 grams (no more than 2 bottles of Axiban, 10 grams each).

The patient should remove the bottle cap, **rapidly** turn the bottle **completely upside down** (i.e., not at an angle) and drop 1-9 drops of oil onto a teaspoon, in accordance with the number of drops required (see below). The bottle should be returned **rapidly** to an upright

position. The patient should carefully insert the teaspoon into the mouth, place it under the tongue, and remove the teaspoon slowly from the mouth, wiping the teaspoon against the underside of the tongue so that the drops remain on the underside of the tongue and the teaspoon comes out "clean". Patients should wait at least 1 minute before swallowing the saliva to allow for submucosal absorption. Swallowing the drops is not dangerous but will lead to a different pharmacokinetic profile including a delayed onset of action. After use, the patient should securely close the bottle with the bottle cap. Note: Holding the bottle at an angle may lead the drops to adhere to the rim of the bottle. If this happens, the patient should stop dispensing, wipe off any remaining oil from the rim of the bottle, wait a minute and resume dispensing using the correct technique.

Most patients will require about 2-6 drops about 3-4 times per day (see below, Titration). No more than 9 drops should be taken in a single intake; if >9 drops are necessary at a single intake then it is recommended to switch to a more concentrated product in order to use fewer drops per intake.

It is preferable not to take medical cannabis on an empty stomach in order to limit the reduction in blood sugar level. About 5 minutes before administering the drops, patients should eat or drink something sweet to counter the reduction in blood sugar level from cannabis. Patients should wait at least 15 minutes after taking Axiban before eating or drinking to ensure adequate absorption. Since food could affect the bioavailability of the drops, it is preferable for the patient to take the medicine each time in the same manner with regard to meals, in order to maintain consistency.

4.3 Contraindications

Prior, current or family history (first degree relative) of psychosis or schizophrenia or schizoaffective disorder, a history of addiction or substance abuse (including cannabis use disorder or addiction to alcohol), use in pregnancy or breastfeeding, use in patients <18 years old, bipolar disease, hypersensitivity to cannabis or coconut oil/palm kernel oil.

In patients with hepatic cancer, it is recommended not to use medical cannabis that contains THC.

Note: Some experts state that, except for hypersensitivity and breastfeeding, these are relative and not absolute contraindications. Therefore, if the decision is made to use medical cannabis in at-risk patients, such as patients with psychosis risk or substance abuse risk or bipolar disease, one should generally choose a CBD-dominant cannabis and monitor closely.

Any patient who cannot be adequately monitored following treatment initiation should not be treated with medical cannabis.

4.4 Special warnings and precautions for use

General: Use caution in patients aged 18-25 years old, patients with significant kidney or liver disease, current depression or anxiety disorder, significant cardiovascular disease (cardiac insufficiency, past or current myocardial infarction or angina pectoris, uncontrolled hypertension, cardiac arrhythmia), immunocompromised patients (relevant for CBD-rich products). Patients being treated for a psychiatric disorder (e.g. PTSD) should be under the care of a psychiatrist and followed up closely.

Use in hypertension and diabetes: Changes in blood pressure in hypertensive patients, and changes in blood glucose in diabetics, should be monitored after initiating therapy and following any dosage increase. Patients with hypertension or diabetes and taking anti-hypertensive medication or anti-hyperglycemic medication, respectively, may need to have their dose of medicine adjusted upon initiation of medical cannabis and following any dosage increase of medical cannabis.

Use in the elderly: Since treatment initiation and any subsequent increase in dosage may be accompanied by somnolence or dizziness, elderly or infirm patients should be cautioned regarding the risk of falling. In addition, the CNS adverse reactions could potentially have an impact on various aspects of personal safety in the elderly, such as the cooking of food and preparation of hot drinks.

Use in pediatrics: Axiban is contraindicated in pediatric patients.

Use in renal or hepatic impairment: Both THC and CBD are metabolized in the liver. The primary metabolites are 11-OH-THC and 7-OH-CBD, respectively. Approximately two-thirds undergoes enterohepatic recirculation and is eliminated in the feces and one-third is excreted in the urine. Thus, systemic exposure is dependent on both renal and hepatic function, and significant impairment of either may lead to an exaggerated or prolonged effect of medical cannabis. Such patients should be closely monitored.

4.5 Interactions with other medicinal products and other forms of interaction

The field of drug interactions with medical cannabis has not been well researched, and many of the drug interactions noted below are theoretical and have not yet been demonstrated clinically. Potential drug interactions are based on either a pharmacokinetic mechanism or a pharmacodynamic mechanism.

Pharmacokinetic interactions:

Both THC and CBD, the main active ingredients in medical cannabis like Axiban, are metabolized in the liver via CYP450 enzymes, such as 2C9 (THC), 2C19 (CBD) and 3A4 (THC and CBD).

Drugs that are strong CYP3A4 inhibitors (e.g., clarithromycin, cyclosporine, erythromycin, itraconazole, ketoconazole, mifepristone, protease inhibitors, verapamil, voriconazole, ombitasvir, paritaprevir, and grapefruit juice) could lead to higher THC and CBD levels, while drugs that are strong CYP3A4 inducers (e.g., carbamazepine, enzalutamide, non-nucleoside reverse transcriptase inhibitors, phenobarbital, phenytoin, primidone, rifampicin, rifabutin, St. John's wort) could lead to lower THC and CBD levels.

It is possible that strong CYP2C9 inhibitors (e.g., amiodarone, clopidogrel, fluconazole, fluorouracil, metronidazole, sulfamethoxazole, valproic acid, and voriconazole) could lead to higher THC levels. Similarly, it is possible that strong CYP2C9 inducers (e.g., barbiturates, carbamazepine, phenytoin, rifampicin, rifabutin, St. John's wort) could lead to lower THC levels.

It is possible that strong CYP2C19 inhibitors (e.g., chloramphenicol, clopidogrel, efavirenz, esomeprazole, fluconazole, fluoxetine, fluvoxamine, isoniazid, modafanil, omeprazole, oxacarbazepine, voriconazole) could lead to higher CBD levels. Similarly, it is possible that

strong CYP2C19 inducers (e.g., barbiturates, carbamazepine, phenytoin, primidone, rifampicin, St. John's wort) could lead to lower CBD levels.

A single case report described a drug interaction between smoking cannabis and warfarin, characterized by an elevated INR. CBD may inhibit CYP2C9, the enzyme involved in the metabolism of warfarin. Monitoring of INR is recommended.

CBD, a cannabinoid indicated for the treatment of refractory pediatric epilepsy, was shown to interact with several anti-epileptic medicines. CBD raised in a dose-proportional manner, the levels of clobazam and N-desmethylclobazam, eslicarbazepine, rufinamide, topiramate, zonisamide, and increased liver enzymes when given together with valproate.

Pharmacodynamic interactions:

a) CNS depressants: Medical cannabis can have a pharmacodynamic drug interaction with other CNS depressant drugs, such as opioids, benzodiazepines, other hypnotics or sedatives, H1 receptor antagonists, and alcohol, increasing the risk or severity of somnolence, dizziness, fatigue, and ataxia or impaired balance. Discontinuation of these drugs or a reduction in their dose should be an aim of therapy with medical cannabis. Concomitant use of alcohol in particular should be discouraged to reduce risks associated with driving and risk of falls. If a patient is scheduled for surgery including the use of an anesthetic, the surgeon and anesthesiologist should be consulted.
b) Muscle relaxants: Care should also be taken when using muscle relaxants or anti-spasmodics (e.g., benzodiazepines, baclofen) since concomitant use with medical cannabis could decrease muscle tone or strength and increase the risk of falls and other accidents.
c) Anti-hyperglycemic medicines: Medical cannabis could have an additive effect on reducing serum glucose levels when given with anti-hyperglycemics. The dose of anti-hyperglycemic may need to be adjusted, particularly upon treatment initiation of medical cannabis and following any dosage increase.
d) Anti-hypertensives: Medical cannabis could have an additive effect on lowering blood pressure when given with anti-hypertensives. The dose of anti-hypertensive may need to be adjusted, particularly upon treatment initiation of medical cannabis and following any dosage increase.
e) Anti-cholinergics: Medical cannabis could have an additive effect (e.g., increase in dry mouth, drowsiness, tachycardia and dizziness), when given with anticholinergic medicines such as tricyclic antidepressants, antihistamines used for allergies.
f) Sympathomimetics: Medical cannabis could have an additive effect (e.g., tachycardia, increase in blood pressure), when given with sympathomimetics including medicines administered topically into the nose or eye, which have a potential for systemic absorption.

4.6 Fertility, pregnancy and lactation

Pregnancy and Breastfeeding: Medical cannabis is contraindicated during pregnancy and breastfeeding according to IMC-GCP. Both female and male patients must use an effective form of contraception not only during medical cannabis use but also for 3 months subsequent to treatment discontinuation. Some cannabis constituents can pass into the breast milk and could adversely affect the baby.

Fertility: In the literature, cannabis use has been associated with a decrease in sperm quantity and quality. The testes are rich in endocannabinoid expression.

4.7 Effects on ability to drive and use machines

Medical cannabis can lead to somnolence, dizziness and several other adverse effects (such as a decrease in judgment and concentration, impaired performance of motor skills and a slowing of the reaction time), which can impair driving ability and the ability to operate heavy/dangerous machinery. This could result in an increase in the risk of accidents. Usually these adverse effects are more prominent at the beginning of therapy and following any increase in dosage.

Transportation Ordinance Section 64b and Transportation Regulations in Israel determine under which conditions it is permissible or forbidden to drive while under therapy with medical cannabis, and one should always act in accordance with these ordinance/ regulations. Patients should be informed that driving not in accordance with the Transportation Ordinance /Regulations and while any level of cannabis or its metabolites may be detected in the blood or urine is a violation of Traffic Ordinance 64b, regardless of driving ability. [Note: Metabolites of cannabis may be found in the urine following last use for up to 21-30 days in long-term users. This is because cannabinoids are highly lipophilic and they accumulate in the fatty tissue. Slow release from the fatty tissue leads to a prolonged terminal elimination half-life of ~24-36 hours for THC and ~18-32 hours for CBD.]

4.8 Undesirable effects

Adverse reactions are categorized as: a) acute reactions, or b) chronic reactions.

Acute adverse reactions

The most frequent acute adverse reactions of medical cannabis upon treatment initiation are mild-moderate dizziness, somnolence and tiredness/fatigue. Patients are likely to feel especially tired at the beginning of therapy since the "relief of stress" once medical cannabis is initiated is often associated with a desire to sleep. Patients should take this into account and be reassured that this is a normal reaction that will subside once the body adjusts. Other frequent reactions are a reduction in blood pressure, increase in pulse or decrease in blood glucose levels. Patients may feel a fast heartbeat or pulse, or palpitations, faintness, nausea, sweating, trembling, weakness because of low blood pressure or glucose levels. Patients should be advised to eat something sweet (e.g., fresh or dry fruit or fruit juice) prior to using medical cannabis in order to prevent these symptoms. (Diabetics should consult with their endocrinologist.)

Other possible acute adverse reactions of medical cannabis include: increase in appetite ("the munchies"), redness in the eyes, headache, stomach ache, dry mouth, dry eyes, blurred vision, impaired balance and motor coordination, and cognitive effects such as impaired memory, train of thought, concentration, judgment, or psychomotor skills, disorientation, euphoria, a feeling of "heaviness" or "spaced out", relaxation, and an altered perception of time and space or a heightened sensation. [Note: Cannabis with a high CBD content and a low THC content is unlikely to lead to euphoria, memory-concentration-judgement impairment, altered perceptions and sensations, etc.]

Most acute adverse events are mild and will abate over time once the body adjusts to the medical cannabis. Cancer patients with changes in the oral cavity (e.g., mucositis) may experience nausea due to the oil in the drop formulation. Local reactions at the site of application are also possible.

If the medical cannabis dose is too high, the patient may experience a larger reduction in blood glucose levels or blood pressure, tachycardia or a fast pulse, and possibly even syncope. If these symptoms do occur, patients should be advised to eat something sweet and to lie down until the reaction subsides. Patients may feel extreme dizziness, somnolence or "tishtush" (altered level of alertness) (Patients should decrease the dose at the next intake.)

At too high a dose of THC, the patient may feel confusion, anxiety or panic. And with very high THC doses, cannabis can rarely trigger psychosis/paranoia/hallucinations/delusions, especially in at-risk patients. Such adverse events generally mandate discontinuation of medical cannabis.

Acute intoxication of recreational cannabis smoking has also rarely been associated with cardiovascular and cerebrovascular events such as angina pectoris, myocardial infarction (via coronary arterial vasospasm) and stroke (via cerebral vasoconstriction). Chronic use may cause bradycardia. Some physicians do not advise medical cannabis use for patients with significant heart disease/arrhythmia.

Chronic adverse reactions

The chronic adverse effects of cannabis are less well established. Chronic cannabis use has been linked to:

- Cognitive impairment (e.g., decrease in memory, attention, IQ) – The evidence is primarily from studies looking at recreational cannabis use in adolescents, when the brain is undergoing active development and so is more vulnerable to cannabis.
- Poor educational outcome, diminished life achievement and life satisfaction, amotivational syndrome – This effect is linked to recreational cannabis use in adolescence.
- Psychoses (including schizophrenia) – The evidence is strongest for those patients with a predisposition to developing psychosis/schizophrenia (e.g., war veterans, patients whose parents had schizophrenia), or exacerbating psychosis/ schizophrenia in patients who already have the disease.
- Depression and anxiety – The literature is "mixed", with some studies - but not others - showing an association between cannabis use and the onset or severity of depression and anxiety. In bipolar patients, cannabis can precipitate mania.
- Decrease in sperm quantity and quality. The testes are rich in endocannabinoid expression.
- Hyperemesis syndrome in heavy users.
- Use disorder – See below.

Overall, most of the long-term effects cited above have been demonstrated in heavy or long-term recreational cannabis users, and it cannot be assumed that the same level of risk exists for patients using cannabis medically. There is good reason to presume that risk is likely to be lower with medical cannabis due to a different pattern and purpose of use (e.g., adult onset of initiation, gradual titration, moderate rather than heavy use, lower THC % and/or

higher CBD %, therapeutic use). But in theory, some risks could also be higher due to concomitant medications or comorbidities that medical patients typically have.

An important study by Ware [COMPASS study] that looked at the safety of medical cannabis (THC 12.5%, median 2.5 g/day) [not Axiban] given to patients with non-cancer pain for 1 year found reassuring safety results. There was no difference in the risk of serious adverse events between the patients given cannabis (n=215) and control patients with pain not given cannabis (n=216). There were also no differences in pulmonary function, neurocognitive function, standard hematology, biochemistry, renal, liver, and endocrine function.

Use disorder: It is estimated that about 9% of cannabis users have a "use disorder", which can include abuse and addiction. Rates are higher in those beginning in adolescence and in frequent users (20%). It is not known what percentage of users of medical cannabis develop a use disorder. Cannabis is often called the "gateway drug" since among people who later use "harder" illicit drugs like heroin, cannabis is often the first illicit drug that people use before "graduating" to "harder" drugs. On the other hand, most people who use cannabis do not go on to use "harder" illicit drugs. (Cannabis is more likely to have an adverse effect as a "gateway drug" if used recreationally during adolescence.) Regarding withdrawal, cannabis withdrawal has been described in the literature. The symptoms can include irritability (even to the point of angry outbursts or aggression), restlessness, anxiety, depression, difficulty concentrating, insomnia and nightmares, shakiness, chills, abdominal pain, sweating, changes in appetite, craving for drug, etc. However, it does not appear to be dangerous like it is for alcohol. It is not clear whether there is withdrawal after discontinuing cannabis used medically. However, as a precaution, it is generally recommended to implement a gradual downward titration when discontinuing therapy in order to prevent temporary bodily, mood and sleep disorders.

Reporting suspected adverse reactions: Reporting suspected adverse reactions after the authorization of the medical cannabis product is important. It allows continued monitoring of the benefit/risk balance of the product. Any suspected adverse events for Axiban should be reported to Rafa: drugsafety@rafa.co.il

4.9 Overdose

There are no recorded deaths due solely to cannabis in the literature, but the possibility of overdose in pediatric patients cannot be definitively excluded. Cannabis is not thought to be associated with respiratory depression like opioids since there are no CB1 receptors in the medulla oblongata (the brain respiratory center). Expected symptoms of overdose are those cited above for an excessive dose (hypotension, tachycardia, hypoglycemia, anxiety, panic or psychotic reactions). In the case of overdose, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL AND MODE OF ADMINISTRATION PROPERTIES

Pharmacology: THC binds to CB1 and CB2 receptors, which are receptors in the body located in the brain and in the periphery that bind the endogenous cannabinoids (anandamide and 2-AG). In contrast, CBD acts primarily by binding to other receptors, which indirectly enhance the effects of the body's own endogenous cannabinoids. THC and CBD have a variety of pharmacological activities and impact a diverse range of physiological processes,

such as analgesia, sleep, appetite, energy expenditure, immune function, seizure suppression, etc. THC possesses psychoactive properties, while CBD does not.

Mode of administration: Medical cannabis can be given via 4 routes of administration: smoking, inhaling (using a vaporizer*), oromucosal (e.g., sublingually), or orally.

*Vaporizers use a smokeless system that heats us the cannabis but does not cause it to combust. It causes the essential oils containing the active ingredients to boil, creating a vapor that can be inhaled. It does not damage the lungs like smoking and it has a less strong smell which dissipates faster than cannabis cigarettes.

A sublingual administration of medical cannabis as for Axiban has 3 advantages: a) a pharmacokinetic advantage, b) a safety advantage, and c) an adherence advantage.

Pharmacokinetics: The inhaled route, whether via smoking or via a vaporizer, is associated with a rapid absorption and high peak levels of THC, which means a relatively fast of action. However, this is followed by a relatively short duration of action. On the other hand, the oral route is associated with a slow absorption and low peak levels, which means a relatively slow onset of action, but with a long duration of action. The oromucosal route provides a pharmacokinetic profile that is in-between that of the inhaled and the oral routes. Thus, the oromucosal route is characterized by an onset of action that is faster than the oral route, but with a duration of action that is longer than the inhaled route, allowing for an optimal pharmacokinetic profile. The oromucosal route is excellent for managing chronic (rather than acute) conditions, and for patients who experience euphoria with the inhalational route.

Safety: Smoked cannabis exposes the patient to the known risks and dangers associated with smoking. Cannabis smoke contains tar, particular matter, carbon monoxide, and carcinogens (for example nitrosamines), which probably increase the risk of a patient developing lung cancer, pulmonary disease (e.g., bronchitis and possibly COPD) and cardiac disease. According to some experts, there is no room for a smoked medicine today in the clinician's armamentarium for treating pain and other cannabis indications. The oral presentation, given as "cannabis cookies", possesses two inherent safety risks. The first is a risk of being mistaken for food and being ingested by persons other than the patient, and specifically children. The second risk relates to pharmacokinetics. Since the onset of action following oral intake is delayed, patients may be tempted to take another dose, potentially leading to an excessive dose. Furthermore, when cannabis is taken orally, it undergoes significant hepatic first-pass and the THC is converted to an active metabolite 11-OH-THC. This means that there is a greater risk of accumulation of pharmacologically active constituents. Therefore, according to the Israeli Ministry of Health, the use of oral cannabis cookies is restricted, and is authorized only for pediatric patients with recalcitrant epilepsy, since these patients may not be able to use cannabis via another route of administration. Sublingual drops do not pose a safety risk to the lungs and are far less likely to be mistaken for food or taken by accident by a non-patient. Furthermore, sublingual administration bypasses a significant hepatic first-pass effect.

Adherence: The inhaled route may be difficult for many patients to use. Smoking may not be acceptable to patients who have not smoked in the past. Smoking also presents the problem of second-hand smoke to persons nearby. A vaporizer costs money, may be cumbersome (depending on its size), and requires education on proper use and maintenance. Both

smoking and using a vaporizer require dexterity and adoption of the correct technique, which may be problematic for elderly and other patients. In contrast, sublingual drops are easy to use, small and discreet, and do not affect persons nearby. They are suitable for patients of all ages, including elderly patients. Furthermore, the Ministry of Health has issued additional limitations regarding the place that one may use inhaled medical cannabis, which do not apply to the sublingual route. Thus, the sublingual method of administration may increase patient adherence.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The MCT (medium chain triglyceride oil) is made from coconut oil and/or palm kernel oil. Axiban also contains Vitamin E.

6.2 Incompatibilities

Axiban should not be mixed with any other substance.

6.3 Special precautions for storage

Axiban should be stored in a cool, dry place, protected from light, up to a temperature of 25C. Axiban should be stored safely out of the reach and sight of children and other non-patients.

6.4 Shelf Life

The shelf life before opening is 12 months, and after opening is 4 weeks.

6.5 Nature of the container

Axiban is available in glass bottles with an integral dropper.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with MOH requirements in regards to controlled materials. Patient should ask a pharmacist how to dispose of product no longer required.

7. MARKETING AUTHORIZATION HOLDER

Manufactured by: Panaxia Pharmaceutical Industries.

Marketed by: Rafa Laboratories

The format of this leaflet was determined by the Israel Ministry of Health.

Note: This document refers only to Axiban and the information presented may not be relevant to other medical cannabis products.