Medicines Adverse Reactions Committee

Meeting date	8/09/2022	Agenda item	3.2.2
Title	**Cannabidiol, potential drug interaction with systemic mTOR and calcineurin inhibitors**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor/ Licence holder**
Everolimus	Afinitor*	Novartis New Zealand
	Certican	Novartis New Zealand
Sirolimus	Rapamune*	Pfizer New Zealand
Ciclosporin	Neoral**	Novartis New Zealand
	Sandimmun, Sandimmun-Neoral	Novartis New Zealand
	Cyclohexal	Hexal New Zealand
	Dexiclo	Douglas Pharmaceutical
	Gengraf	Abbott Laboratories
Tacrolimus	Tacrolimus Sandoz*	Novartis New Zealand
	Prograf, Prograf-XL	Research Associates
	Tacrolimus Mylan	Viatris Limited
Cannabidiol +/-	Sativex	Chiesi New Zealand/ Emerge Health
Tetrahydrocannabidiol	RUA	RUA Bioscience
	Tilray	CDC Pharmaceuticals
	SubDrops	Helius Therapeutics
	EvalaCann	Cannasouth Bioscience
	Kikuya	MW Pharma Limited
	ANTG	MW Pharma Limited
	Medium THC Shishkaberry	JC logistics

PHARMAC funding	Fully funded**: Ciclosporin Funded via special authority*: Everolimus, Sirolimus, Tacrolimus Medicinal cannabis products are not funded
Previous MARC meetings	Topical pimecrolimus and the risk of malignancy: 125th and 129th MARC meeting
International action	The European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) requested new product information wording for systemic mTOR and calcineurin inhibitors. Updates are to include the drug interaction with cannabidiol leading to increase mTOR and/or calcineurin inhibitor serum level increase and toxicity.

<table>
<tr><td></td><td>https://www.ema.europa.eu/en/documents/prac-recommendation/new-product-information-wording-extracts-prac-recommendations-signals-adopted-7-10-march-2022-prac_en.pdf</td></tr>
<tr><td>Prescriber Update</td><td>Medicinal Cannabis Scheme- now operational (June 2020):
Medicinal Cannabis Scheme- Update from the Ministry of Health (March 2020)
Medicinal Cannabis Scheme- Update from the Ministry of Health (December 2019)
Medicinal Cannabis Scheme- Update from the Ministry of Health (September 2019)
Medicinal Cannabis Update (March 2018)
Prescribing Cannabis-based products (June 2017)
Access to Medicinal Cannabis (December 2015)</td></tr>
<tr><td>Classification</td><td>Prescription medicine</td></tr>
<tr><td>Usage data</td><td>Table 1: Number of people with at least one dispensing of a mTOR or calcineurin inhibitor per year, by chemical, 2016-2020.
<table>
<tr><th></th><th>Everolimus</th><th>Sirolimus</th><th>Ciclosporin</th><th>Tacrolimus</th><th>Total</th></tr>
<tr><td>2016</td><td>7</td><td>94</td><td>2412</td><td>1665</td><td>4,178</td></tr>
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<tr><td>2020</td><td>11</td><td>152</td><td>2829</td><td>2323</td><td>5,315</td></tr>
</table></td></tr>
<tr><td>Advice sought</td><td>The Committee is asked to advise:
Whether the available evidence supports a clinically significant drug-drug interaction between cannabidiol and all systemic mTOR and calcineurin inhibitors?
If so, does the wording in the data sheets for all products (mTOR, calcineurin inhibitor, and cannabidiol) need to be updated?
Does this topic need further communication other than MARC's remarks in Prescriber Update?</td></tr>
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1 PURPOSE

In March 2022, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommended that product information for systemic mammalian target of rapamycin (mTOR) and calcineurin inhibitors be updated to include information on a drug interaction with cannabidiol. The interaction may result in increased serum levels and toxicity of mTOR and calcineurin inhibitors.

The PRAC review arose from a phase 1 open-label pharmacokinetic drug-drug interaction trial to investigate the effect of cannabidiol on the pharmacokinetics of other medicines including everolimus (study ID GWCP19195). The current evidence on whether an interaction occurs with all systemic mTOR and calcineurin inhibitors is limited. Since the adverse effects of a potential interaction could be serious; the MARC is asked to review the current information and advise on this safety concern.

2 BACKGROUND

2.1 Availability, indications, mechanism of action

2.1.1 Mammalian target of rapamycin (mTOR) inhibitors

mTOR inhibitors are prescription medicines indicated for the prophylaxis of organ rejection in kidney transplant recipients, and treatment of renal cell carcinoma, neuroendocrine tumours of pancreatic origin and subependymal giant cell astrocytoma's [1, 2]. In New Zealand, both everolimus and sirolimus are available and funded via PHARMAC special authority.

mTOR is a key serine-threonine kinase that plays a central role in the regulation of cell growth, proliferation, and survival. The regulation of mTOR signalling is complex and modulated by mitogens, growth factors, energy, and nutrient availability. The inhibition of mTOR results in the blockage of several signal transduction pathways, the net result is inhibition of lymphocyte activation and therefore immunosuppression [1, 2].

2.1.2 Calcineurin inhibitors

Calcineurin inhibitors are immunosuppressant agents that supress T-cell activation, T-helper-cell dependant B-cell proliferation, and the formation of inflammatory lymphokines (interleukin-2, -3, and γ-interferon). Indications for this class of medicine include the prevention and treatment of solid organ transplant and bone marrow transplant rejection, prevention, and treatment of graft-versus-host disease, systemic therapy for patients with atopic dermatitis, psoriasis, rheumatoid arthritis, nephrotic syndrome, and endogenous uveitis. Unapproved uses include severe acute ulcerative colitis refractory to corticosteroid treatment [3, 4].

Systemic calcineurin inhibitors include ciclosporin, which is available on prescription with no restrictions to access, and tacrolimus, which is available to patients who meet PHARMAC funding criteria. Topical tacrolimus and pimecrolimus are also available in New Zealand but will not be discussed in this report.

2.1.3 Cannabidiol

The *Cannabis sativa* (cannabis) plant contains a wide variety of chemical compounds (cannabinoids) including delta-9-tetrahydrocannabinol (THC), the major psychoactive constituent of cannabis, and the non-psychoactive component cannabidiol (CBD) [5]. The biological effects of cannabinoids are understood to be mediated by cannabinoid receptors in the endocannabinoid system (ECS) [6]. The ECS is comprised of cannabinoid receptors, endocannabinoids, and the enzymes involved in the synthesis and degradation of endocannabinoids. The ECS is a widespread neuromodulatory system involved in central nervous system development, synaptic plasticity, and the response to endogenous and environmental stimuli [6]. Although there is growing interest in the safety and efficacy of both THC and CBD products, the focus of this paper will be on CBD.

CBD is thought to be a potential therapeutic target for a variety of conditions such as epilepsy, anxiety, chronic pain, relief of cancer related symptoms, and treatment of substance abuse [7]. However, the current evidence for CBD for treatment of these conditions is limited. Issues identified in the existing safety and efficacy data

include potential bias, small sample sizes and trial duration, design heterogeneity, lack of effective blinded RCTs, difference in doses/formulations and product constituents between and within trials [8].

Sativex, a combination CBD and THC oromucosal spray is the only Medsafe approved medicinal cannabis product available in New Zealand. Sativex is indicated as an add-on treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis, who have not responded adequately to other anti-spasticity medicines, and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy [9]. Epidyolex is a pharmaceutical grade CBD oral solution, which has been approved by the EMA as an adjunct therapy for seizures associated with tuberous sclerosis complex, or in Lennox-Gastaut syndrome and Dravet syndrome in conjunction with clobazam in patients 2 year of age and older [10]. Epidyolex is not approved or available in New Zealand.

Medicinal cannabis products are available under the Misuse of Drugs Act 1975 and Misuse of Drugs (Medicinal Cannabis) Regulations 2019. These products meet minimum quality standards and are verified by the Medicinal Cannabis Agency. They are unapproved products and have not undergone clinical efficacy and safety evaluations [11]. CBD products are available in different dosage forms, strengths, and varying THC/CBD concentrations. Because they are unapproved, these products do not have published data sheets. Prescribers rely on data sheets to guide clinical decisions in practice. Without readily available accurate information, healthcare professionals maybe unaware of the safety concerns and potential DDIs associated with cannabis products.

Comment:
International changes in policies and regulatory status of cannabis have contributed to research and the increasing use of medicinal cannabis products. Although data on the safety and efficacy remains limited, CBD products are typically considered to be 'safer' than THC containing products. Medicinal cannabis is not recommended as a first-line treatment for any indication.

Epidyolex is not approved or available in New Zealand. It is mentioned here because the DDI with mTOR inhibitors was first identified in a clinical trial of Epidyolex (cannabidiol) and everolimus.

2.2 Usage

Usage data for systemic mTOR and calcineurin inhibitors is shown in Table 1. CBD products available on prescription are not funded. Therefore, usage data is not captured by the Ministry of Health Pharmaceutical Data web tool.

The Ministry of Health survey on cannabis use found that approximately 10% of adults reported cannabis use within the last 12 months regardless of legal status. Of these users, 40% reported that they self-medicate with cannabis to treat various medical conditions [12] .

Table 1: Number of people with at least one dispensing of a mTOR or calcineurin inhibitor per year, by chemical, 2016-2020.

	Everolimus	Sirolimus	Ciclosporin	Tacrolimus	Total
2016	7	94	2412	1665	**4,178**
2017	7	105	2585	1817	**4,514**
2018	10	125	2653	1961	**4,749**
2019	11	139	2778	2160	**5,088**
2020	11	152	2829	2323	**5,315**

Source: Ministry of Health. Pharmaceutical data web tool. URL https://minhealthnz.shinyapps.io/pharmaceutical-data-web-tool (accessed 19 July 2022).

Comment:
The true incidence of cannabis use is likely underestimated in survey responses. It is important to note that the Ministry of Health Cannabis use survey was conducted in 2012/2013 and may not reflect current cannabis use in New Zealand.

2.3 Nature of the safety concern

2.3.1 Summary of the safety concern

CBD has been implicated in several drug-drug interaction (DDI) reports involving mTOR and/or calcineurin inhibitors. mTOR and calcineurin inhibitors have high pharmacokinetic and pharmacodynamic variability. Patients require close monitoring to ensure drug levels are maintained within their therapeutic range. Ciclosporin undergoes metabolism via multiple pathways. Everolimus, sirolimus, and tacrolimus are substrates of, and undergo metabolism by, cytochrome P450 (CYP450) isoenzymes and/or P-glycoprotein (P-gp). These pathways are associated with many DDIs [1-4].

Alterations in the exposure to mTOR and calcineurin inhibitors is concerning in terms of drug ineffectiveness and/or drug toxicity. Variability in exposure has been shown to negatively affect long-term outcomes in solid organ transplant recipients [13]. A meta-analysis of cannabis use in kidney transplant recipients found cannabis use was associated with an increase in death-censored graft failure (a rapid loss of graft function), with pooled odds ratio of 1.72 (95% CI 1.13-2.60). However, cannabis use was not significantly associated with all-cause allograft failure or mortality [14].

Reports of elevated mTOR/calcineurin serum drugs levels following concomitant use of CBD have been published in the literature, patients present with signs and symptoms of elevated serum creatinine, encephalopathy, and altered mental status. The exact mechanism for this possible DDI is unknown, authors hypothesise this is due to a pharmacokinetic interaction between CBD and mTOR/calcineurin inhibitors [13].

2.3.2 Mechanism of the potential DDI

Cytochrome P450 (CYP450) enzymes are important drug metabolising enzymes found in the liver. Six isoenzymes metabolize up to 90 percent of drugs. These include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5. Isoenzymes can be inhibited or induced by drugs, resulting in clinically significant DDIs that may cause adverse reactions or therapeutic failures [15].

Efflux transporters such as P-gp also play an important role in drug transport. Intestinal P-gp transports substate drugs back into the lumen, decreasing their absorption. Drugs which induce P-gp can reduce the bioavailability of other drugs, and inhibitors of P-gp can increase the bioavailability of susceptible drugs. Many drugs transported by P-gp are also metabolised by CYP450 enzymes, giving rise to potential DDIs [16].

The pharmacokinetics and pharmacodynamic effects of cannabis products depend on the formulation and route of administration. CBD undergoes hepatic metabolism through CYP450 enzymes, particularly by the isoforms CYP2C19 and CYP3A4. It is converted to primary active metabolite 7-hydroxy-CBD (7-OH-CBD) by CYP2C19, and further to inactive metabolites through uridine diphosphate glucuronosyltransferase (UGT) enzymes (Figure 1) [17].

The product information for Sativex and Epidyolex suggest CBD has the potential to affect other drugs and medicines [9, 10]. Mechanisms include inhibition of CYP3A4 at clinically relevant concentrations and inhibition of the uridine diphosphate-glucuronyltransferase (UGT) enzymes UGT1A9 and 2B7 [9, 10]. UGT enzymes catalyse glucuronidation to aid drug excretion. Inhibition of UGTs increases the bioavailability of a substrate by reducing the amount of substrate that is excreted.

Figure 1: Metabolism pathways of cannabidiol

Source: Landmark et al. 2020. *Pharmacology and drug interactions of cannabinoids.* DOI: https://onlinelibrary.wiley.com/doi/full/10.1684/epd.2019.1123 (accessed 17 May 2022)

A phase 1 study investigating the pharmacokinetics of CBD found that CYP3A4 inhibitors increase systemic exposure of CBD and 7-OH-CBD, and CYP3A4 inducers decrease the exposure of both CBD and 7-OH-CBD. Careful titration of CBD is recommended when administered with substances that inhibit or induce CYP3A4. Co-administration with rifampicin, a strong CYP3A4 and CYP2C19 inducer reduced the Cmax of CBD by 52%. Co-administration with omeprazole, a CYP2C19 inhibitor did not change the pharmacokinetic parameters of CBD [18]. CDB has been found to decrease *in vitro* activities of CYP3A5/7, 2D6, 2C9, 2A6, 2B6, 1A1, 1A2, 1B1, and 2J2. However, the *in vivo* and clinical relevance of these findings have not been established [19].

CBD and its active 7-OH-CBD metabolite have no predicted activity on drug transporters. However, the inactive, hydroxylated, 7-COOH-CBD is a substrate for P-gp and an inhibitor of breast cancer resistance protein (BCRP) and the bile salt export pump (BSEP) at clinically relevant concentrations [19]. As the metabolite is inactive, no clinically relevant effects are expected. However, BCRP and BSEP play roles in the efflux of drugs from tissues into excretion pathways. Inhibition of BCRP and BSEP may result in increased distribution of a substrate drug into tissues and decreased excretion, potentially increasing the risk of drug accumulation and adverse effects [19].

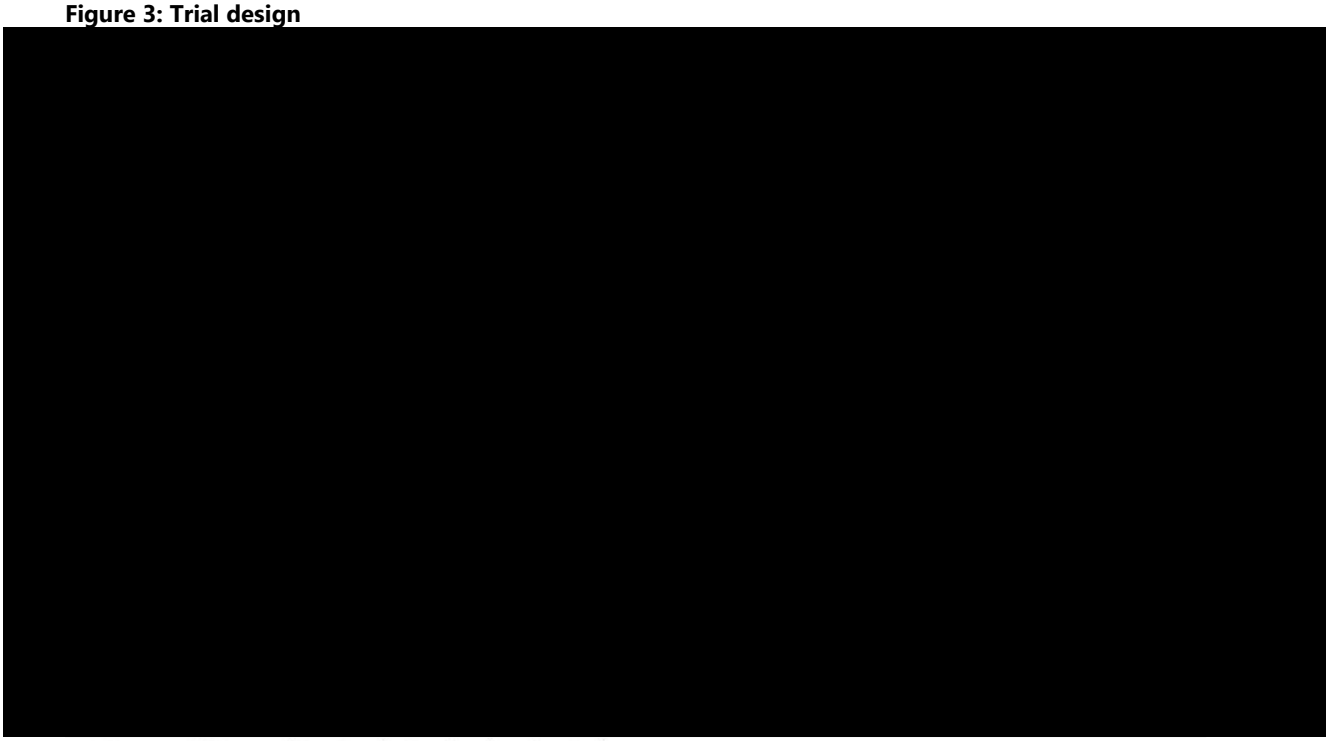
An *in vitro* study conducted by Zhu et al suggests that CBD inhibits P-gp mediated drug transport, and therefore could potentially influence the absorption and disposition of other co-administered compounds that are P-gp substrates. Zhu notes that the clinical relevance of this study has not been established and additional studies are required to understand the extent of CBD inhibition of P-gp [20].

There are two major studies that investigate pharmacokinetic drug interactions with CBD (Patsalos et al and Gaston et al), they are summarised below.

2.3.2.1 Patsalos et al 2020 [21]

The authors reviewed six trials that investigated potential interactions between CBD and enzymes involved in drug metabolism of common antiepileptic drugs (AEDs). The trials reviewed consist of four phase 1 open-label, fixed-sequence trials in healthy volunteers, and two phase 2, randomised, double-blind, placebo-controlled trials in patients with epilepsy. The trial designs and concomitant drugs are summarised on Figure 3. CBD, clobazam, stiripentol, and valproate all interact with and utilise CYP and UGT enzymes, there is potential for DDIs between CBD and these AEDs. The effect of CBD on other drugs on common enzymes that metabolise drugs were investigated using the standard probes and specific inhibitors and inducers. These include midazolam, a probe used to measure CYP3A4 activity, rifampicin, an inducer of CYP3A4 and CYP2C19, itraconazole, an inhibitor of CYP3A4, and fluconazole, an inhibitor of CYP2C19.

Figure 3: Trial design



Source: Patsalos et al. 2020. *Clinical implications of trials investigating drug-drug interactions between cannabidiol and enzyme inducers or inhibitors or common antiseizure drugs.* DOI: 10.1111/epi.16674 (accessed 20 May 2022)

A total of 142 healthy volunteers and 55 patients with epilepsy were enrolled across the six trials and administered a CBD dose of 750mg twice daily or 20mg/kg/day. Pharmacokinetic assessments were measured via blood samples taken at predefined intervals, and plasma concentrations of analytes were predetermined using liquid chromatography and mass spectrometry. The primary parameters measured were maximum observed plasma concentration (Cmax), area under the concentration-time curve over the dosing interval (AUCtau), and area under the concentration-time curve up to time t, where t is the last point with a concentration above the lower limit of quantification (AUC0–t). Safety and tolerability assessments across the trial included treatment-emergent adverse events, clinical laboratory evaluations, vital signs, electrocardiograms, physical examinations, and the Columbia-Suicide severity rating scale questionnaire. The results from the pharmacokinetic studies are pictured in Figures 4-6.

Figure 4: Treatment ratio for the pharmacokinetic effect of CBD on exposure to midazolam and 1-hydroxymidazolam in healthy volunteers

Figure 5: Treatment ratio for the pharmacokinetic effect of rifampicin, itraconazole, or fluconazole on exposure to CBD in healthy volunteers

Figure 6: Treatment ratio for the pharmacokinetic effect of CBD on exposure to clobazam, N-desmethylclobazam, stiripentol, valproate, and 2-propyl-4-pentenoic acid in health volunteers and patients with epilepsy.

Figures 4-6 source: Patsalos et al. 2020. *Clinical implications of trials investigating drug-drug interactions between cannabidiol and enzyme inducers or inhibitors or common antiseizure drugs.* DOI: 10.1111/epi.16674 (accessed 20 May 2022_

The trials summarised in the review suggest that CBD is unlikely to cause clinically relevant DDIs with other medicines metabolised by CYP3A4 however, coadministration of CBD with a strong CYP3A4 or CYP2C19 inducer may decrease systemic exposure to CBD and its active metabolite 7-OH-CBD, the clinical significance

of this interaction remains unknown. Potent inhibition of these isoenzymes did not markedly impact CBD exposure in a clinically important manner. Of all the DDIs investigated, a single and potentially clinically significant interaction was identified when CBD is co-administered with clobazam. This resulted in a bidirectional DDI that increased levels of the active metabolites for both compounds.

Based on pharmacokinetic parameters alone, dose adjustments are not necessary when CBD is given concomitantly with stiripentol or valproate, although an independent effect of increased dose-related elevations in transaminase levels should be considered when CBD and valproate are combined.

Comment:
This article highlights that CBD may not have clinically significant DDIs with drugs that are commonly linked with pharmacokinetic DDIs. However, the relevance of these findings when CBD is co-administered with an mTOR or calcineurin inhibitor remains unknown.

2.3.2.2 Gaston et al 2017 [22]

Authors at the University of Alabama Birmingham conducted a prospective open-label study investigating CBD (Epidiolex) as a potential add-on therapy for the treatment of treatment-resistant epilepsy in children and adults. The purpose of the study was to identify which AEDs potentially interact with CBD based on serum drug level changes, and in turn, if these potential interactions were clinically meaningful.

There were 39 adults and 42 children enrolled in the study, all on multiple concomitant AEDs. Participants were initiated on oral Epidiolex at a dose of 5mg/kg/day and titrated up to a maximum dose of 50mg/kg/day. Dose adjustments were based on participants response to treatment and tolerability. Patients underwent monitoring of serum AED levels to identify possible interactions, changes in drug levels and possible clinically significant relationships.

The authors used the Mixed Procedure analysis to control for nonuniform changes in both CBD dose and AED doses (Figure 8). Linear increases in serum levels of topiramate ($p < 0.001$), rufinamide ($p = 0.004$), and N-desmethylclobazam ($p < 0.001$), and linear decreases in levels of clobazam ($p < 0.001$) with increasing CBD dose were seen in combined paediatric and adult. In addition, a significant increase in serum levels of zonisamide ($p = 0.017$) and eslicarbazepine ($p = 0.039$) with increasing CBD dose was seen in the adult arm only. There were no significant changes in drug levels with CBD dose titration in the other AEDs analysed (valproate, levetiracetam, phenobarbital, clonazepam, phenytoin, carbamazepine, lamotrigine, oxcarbazepine, ethosuximide, vigabatrin, ezogabine, pregabalin, perampanel, and lacosamide). In some cases, particularly with valproate and clobazam certain adverse effects were noted (sedation and elevation of liver function tests) which required weaning of AED doses.

Figure 8: AED level analysis

Source: Gaston et al. 2017. *Interactions between cannabidiol and commonly used antiepileptic drugs.* DOI: 10.1111/epi.13851 (accessed 20 June 2022)

Comment:
The study introduces potential pharmacokinetic interactions with CBD and commonly used AEDs in the treatment of epilepsy. Additional formal pharmacokinetic studies under controlled conditions are required to confirm the interactions and investigate any adverse events that arise from a DDI.

It is important to consider how CBD and its metabolites can influence the drug transport system and the pharmacokinetic properties of other drugs. Because mTOR and calcineurin inhibitors undergo metabolism by CYP3A4 and P-gp, there is a potential for pharmacokinetic DDIs when patients are exposed to CBD.

Comment:
There are biologically plausible mechanisms for which CBD can contribute to DDIs. Current *in vivo* and *in vitro* studies investigating CBD and DDIs have methodological flaws and confounders, which limit their interpretation Additional research is required into the clinical significance of CBD mediated DDIs. There are no preclinical or clinical studies that have investigated the effect of CBD when co-administered with mTOR or calcineurin inhibitors.

2.3.3 DDI database information

2.3.3.1 Stockley's Drug Interaction Checker

Stockley's online interaction checker lists 95 results for possible interactions with CBD (Annex 1) [23]. Of these, 16 DDIs recommended a dose adjustment and/or close monitoring, 29 interactions required additional guidance about possible adverse effects and/or considered some monitoring, and 50 interactions are classed as no interaction/not clinically significant.

There were no interactions listed for CBD and systemic mTOR/calcineurin inhibitors. Generally, listed interactions were mild to moderate in severity and are based on theoretical evidence. Only interactions with Rimimazolam, Valproate, Difelikefalin, and Ganaxolone are considered severe.

2.3.3.2 Lexicomp Drug Interactions

Lexicomp is a collection of clinical databases and decision support tools available on UpToDate [24]. Drug interactions are given a risk-based assessment based on the evidence and severity of the interaction. An interaction between CBD and sirolimus is given an X rating (avoid concomitant use), interactions with a C rating (monitor therapy) are listed for CBD use with ciclosporin, everolimus and tacrolimus.

Comment:
There are inconsistencies between different resources that healthcare professionals may use when searching for information on CBD interactions. Often, the interactions listed are based on limited and/or poor-quality evidence, which makes clinical interpretation difficult.

2.4 Actions taken by the PRAC

During routine signal detection activities, the PRAC identified the interaction between CBD and systemic tacrolimus resulting in increased serum levels and tacrolimus toxicity as a safety signal. In March 2022, the PRAC discussed this signal and considered the evidence sufficient to request inclusion of this DDI into the product information (Summary of Product Characteristics SPC and Package Leaflet) for all systemic mTOR and calcineurin inhibitors [25]. Annex 2 summarises the proposed SPC wording changes by medicine, the new wording is underlined. Changes to the text were proposed for section 4.4 Special warnings and precautions for use and/or section 4.5 Interactions with other medicinal products and other forms of interactions.

2.5 Data sheets

2.5.1 mTOR and calcineurin inhibitors

A review of the current product information/data sheets for systemic mTOR and calcineurin inhibitors identified inconsistencies in the information provided on a possible DDI with CBD. There are differences in the product information wording seen for individual medicines, across the drug class, and for the same product in different countries. Table 2 provides a summary of the data sheet review.

Table 2: Comparison of international mTOR and calcineurin inhibitors innovator product information: contains CBD interaction (yes/no) as of 10 August 2022.

Active ingredient	Region				
	NZ[a]	Australia[b]	USA[c]	UK[d]	EU[e]
Everolimus (Afinitor)	No	No	No	Yes	Yes
Sirolimus (Rapamune)	Yes	Yes	No	No	Yes
Ciclosporin (Neoral)	No	No	No	Yes	Yes
Tacrolimus (Prograf)	No	No	No	Yes	Yes

a. Available at: https://www.medsafe.govt.nz/Medicines/infoSearch.asp

b. Available at: https://www.ebs.tga.gov.au/

c. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

d. Available at: https://www.medicines.org.uk/emc/

e. Available at: https://www.ema.europa.eu/en/medicines

In New Zealand, the data sheet for Rapamune (sirolimus) is the only mTOR inhibitor that currently includes information on a DDI with CBD. The following statement is included in section 4.5.

> **Interactions with other medicines and other forms of interactions:**
> **4.5.2 Cannabidiol**
> There have been reports of increased blood levels of sirolimus during concomitant use with cannabidiol. Caution should be used when cannabidiol and Rapamune are co-administered, closely monitor sirolimus blood levels and for adverse events suggestive of sirolimus toxicity.

The DDI is not mentioned in the New Zealand data sheets for everolimus, ciclosporin or tacrolimus.

2.5.2 Cannabidiol products

The New Zealand data sheet for Sativex does not list specific interactions with individual medicines or classes of drugs. Section 4.5 of the data sheet does recognise the potential for Sativex to affect other drugs/medicines through the CYP450 pathway or inhibition of UGT enzymes. mTOR and calcineurin inhibitors are not listed as interacting medicines [9].

The EU Epidyolex Summary of Product Characteristics (SPC) notes that interactions may occur with CYP3A4 or CYP2C19 inhibitors, UGT inhibitors, concomitant antiepileptic treatments, and sensitive P-gp substrates given orally. Relevant sections of the data sheet where an mTOR or calcineurin inhibitor is mentioned are summarised below [10].

> **4.5 Interactions with other medicinal products and other forms of interaction**
> Everolimus
> Coadministration of cannabidiol (12.5 mg/kg twice daily) with the P-gp and CYP3A4 substrate everolimus (5 mg) in a healthy volunteer study led to an increase in everolimus exposure of approximately 2.5-fold for both Cmax and AUC. The mechanism for this interaction is believed to be inhibition of intestinal P-gp efflux, leading to increased bioavailability of everolimus, because cannabidiol did not affect midazolam exposure in another interaction study. The half-life of everolimus was not affected, confirming the lack of systemic inhibitory effects of cannabidiol on P-gp and CYP3A4 activity. When initiating cannabidiol in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dosage accordingly. When initiating everolimus in patients taking a stable dosage of cannabidiol, a lower starting dose of everolimus is recommended, with therapeutic drug monitoring.
> Sensitive P-gp substrates given orally
> Coadministration of cannabidiol with orally administered everolimus, a P-gp and CYP3A4 substrate, has increased everolimus bioavailability likely due to inhibition of intestinal P-gp efflux of everolimus. Increases in exposure of other orally administered sensitive P-gp substrates (e.g., sirolimus, tacrolimus, digoxin) may occur on coadministration with cannabidiol. Therapeutic drug monitoring and dose reduction of other P-gp substrates should be considered when given orally and concurrently with cannabidiol.

3 SCIENTIFIC INFORMATION

3.1 Published literature: CBD and DDIs

3.1.1 Ebrahimi-Fakhari et al 2020 [26]

The authors conducted a retrospective review of patients with tuberous sclerosis complex (TSC) treated with everolimus or sirolimus and CBD at Cincinnati Children's Hospital medical Centre. Patients with TSC have constitutive activation of mTOR resulting in hamartomas in various organs. Some patients with TSC also have medically intractable epilepsy and epileptic encephalopathies. Everolimus and sirolimus have shown activity against some manifestations of TSC.

A total of 25 patients were identified (18 everolimus patients and seven sirolimus patients), the mean age of CBD treatment initiation was 17 years (range: 3 to 45 years). All patients had a clinically defined diagnosis of TSC. Clinical information, mTOR dosing and trough levels, CBD dosing, concomitant antiepileptic drugs, safety laboratory studies, and adverse events were reviewed at baseline and after initiation of CBD. Follow up trough mTOR inhibitor levels were drawn after a therapeutic CBD dose of 5-20 mg/kg/day.

After CBD treatment, mTOR inhibitor levels were significantly higher in 76% of patients (*P*=0.0003). The median change from baseline was +9.8 ng/mL for everolimus and +5.1 ng/mL for sirolimus (Figure 2). Adverse events were reported in 40% of patients and included diarrhoea, drowsiness, increased and severe mouth sores, acne, ankle swelling. There were no severe adverse events reported.

Figure 2: Comparison of mTOR inhibitor level ng/mL before and after co-administration with CBD.

Source: Ebrahimi-Fakhari et al. 2020. *Cannabidiol elevates mechanistic target of rapamycin inhibitor levels in patients with tuberous sclerosis complex.* DOI: 10.1016/j.pediatrneurol.2019.11.017 (accessed 15 July 2022)

The authors report that concomitant CBD administration resulted in increased serum levels of everolimus and/or sirolimus. Some patients experienced doubling or tripling of their mTOR inhibitor trough following the addition of CBD. In some cases, this resulted in clinical toxicity and laboratory abnormalities. The findings highlight the importance for clinicians to be aware of a possible interaction between CBD and mTOR inhibitors, patients may require dose changes to their medications in order to prevent mTOR inhibitor toxicity.

Comment:
The supplementary information for this paper was not accessible. It would be interesting to see the concomitant drugs used in participants to see whether changes in mTOR levels could be attributed to other administered medicines. Although this study has a small participant group, the findings do show a clinically significant increase in mTOR inhibitor levels associated with CBD use. Additional large prospective studies of CBD and mTOR inhibitors that assess the optimal dose reduction (of either medicine) to reduce the risk of toxicity would be helpful.

At the time of the literature search, no other studies focused on CBD DDIs with mTOR inhibitors, the remaining literature investigated CBD DDIs with antiepileptic drugs.

3.1.2 Gilmartin et al 2021 [27]

The authors conducted a review of Cochrane, PubMed, and Embase from 1 January 2015 to 30 April 2020 for publications discussing interactions between CBD and antiseizure drugs. Thirty studies met the inclusion criteria for review, pharmacokinetic interactions were identified between CBD and brivaracetam, clobazam,

eslicarbazepine, lacosamide, gabapentin, oxcarbazepine, phenobarbital, potassium bromide, pregabalin, rufinamide, sirolimus/everolimus, stiripentol, tiagabine, topiramate and zonisamide. Of these pharmacokinetic interactions, clobazam, its active metabolite (N-desmethylclobazam), brivaracetam and sirolimus/ everolimus have been found to have their serum concentrations altered beyond the therapeutic range.

Source: Gilmartin et al. 2021. *Interaction o cannabidiol with other antiseizure medications: a narrative review.* DOI: 10.1016/j.seizure.2020.09.010 (accessed 7 July 2022)

Comment:
Although this review primarily focuses on DDIs for antiseizure medicines, the authors did find a statistically significant interaction with CBD and sirolimus/everolimus. The reference article for this interaction was the article by Ebrahimi-Fakhari discussed above. Overall, the review shows DDIs occur between CBD and antiseizure medicines and therefore concurrent use can increase the risk of harm.

Although sirolimus and everolimus are not indicated for the prevention and/or treatment of seizures, they have been included in the study by the authors.

3.2 Case reports

3.2.1 Leino et al 2019 [13]

This article describes a case report of a significant DDI between CBD and tacrolimus. The 32-year-old woman on tacrolimus for interstitial nephritis with a medical history of refractory epilepsy entered into a CBD clinical trial. For one year prior to trial entry, her tacrolimus dose and serum levels had been stable. Her baseline laboratory results included a mean tacrolimus blood level of 6.1ng/mL, and serum creatinine (Scr) of 1.2mg/dL.

Following a placebo period, she entered the open-label study on day 100 (Figure 9) and received increasing doses of CBD. Over a 10-day period, seizure frequency improved but the patient developed signs of tacrolimus toxicity. Tacrolimus was empirically held until Scr normalised and restarted at a lower dose. On day 282 the dose of CBD was gradually increased, again Scr rose, and tacrolimus was reduced further (Figure 10). Other potential causes of increased tacrolimus trough levels were considered: concomitant medicines were unchanged, there were no known changes to tacrolimus administration such as formulation, relationship to food, or adherence reported by the patient and/or caregiver. Potential adverse effects were monitored, and diarrhoea (a common adverse effect noted with CBD) was not reported. The authors suspect CBD mediated inhibition of CYP3A4 and/or P-gp led to increases in tacrolimus serum levels and toxicity.

Figure 10: Tacrolimus dosing, trough levels, and Scr in relation to CBD initiation

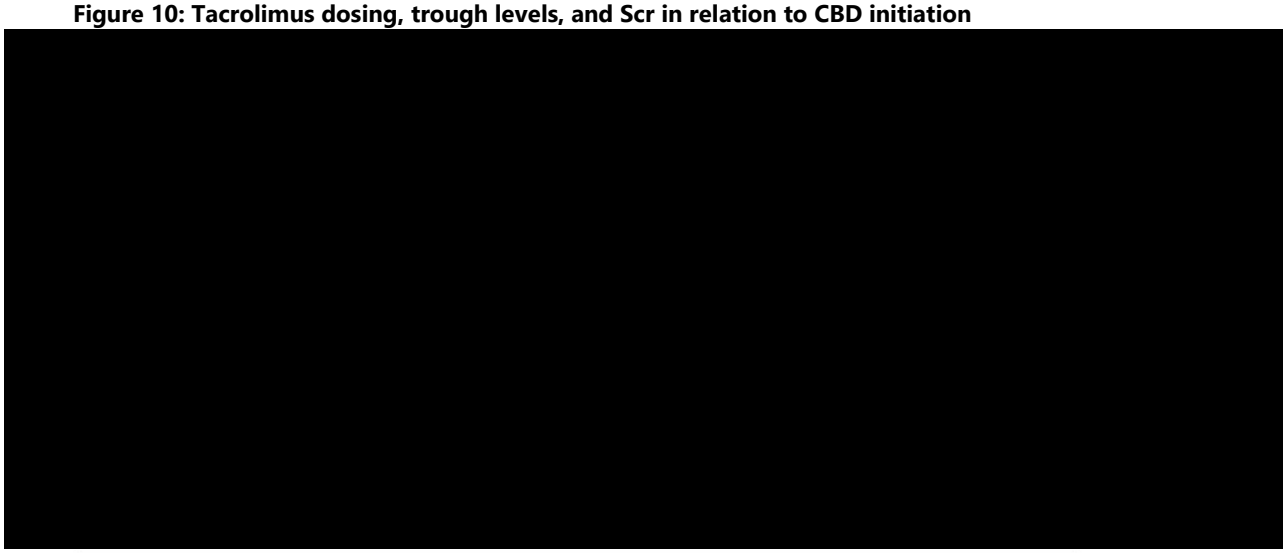


Figure 9-10 source: Leino et al. 2019. *Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus.* DOI: 10.1111/ajt.15398 (accessed 7 June 2022)

Comments:
The authors were unable to obtain the patients CBD levels during the study period and therefore could not assess the degree of CBD exposure that resulted in the change in tacrolimus level. Additional long-term follow up information was not available.

3.2.2 Wiemer-Kruel et al 2019 [28]

The authors describe a case of increasing everolimus blood trough levels following CBD use in a 6.5-year-old patient with a Tuberous Sclerosis Complex mutation. After three years of everolimus treatment for pharmaco-resistant focal epilepsy and severe ventricular dysrhythmia, the patient was initiated on CBD for refractory tonic clonic seizures. The daily dose of CBD started at 200mg and was titrated up to 500mg. The patient's prior everolimus trough levels were stable and ranged from 4-5 mcg/L. After 6 weeks of CBD, everolimus trough

increased to 12 mcg/L, the dose of everolimus was halved but trough levels rose again to 16 mcg/L. The authors suspect the interaction may be due to inhibition of CYP450 enzymes, and although the patient did not report any adverse events, clinicians should be reminded of possible DDI's with CBD use.

Comment:
As only the abstract is available, the information provided in the article is limited. Potential confounders were not discussed.

3.2.3 Hauser et al 2018 [29]

Authors describe a case of tacrolimus toxicity secondary to subtherapeutic drug levels in a post allogeneic hematopoietic stem cell transplant (HSCT) patient using inhaled and edible marijuana. The patient, a 67-year-old man with relapsed follicular lymphoma was admitted to hospital for a match-related HSCT. His pretransplant hospital course was uneventful and transplant was uncomplicated. He was started on a continuous tacrolimus infusion (1.8 mg/kg) with a goal serum level of 8-12 ng/mL.

Tacrolimus dose was reduced due to serum levels being persistently above target, on day 10 the patient admitted to edible cannabis use and traces of THC noted in the urine toxicology screen. On day 14 the patient was transferred to oral tacrolimus, a second toxicology screen came back positive for THC on day 20 and serum tacrolimus levels spiked to 43.8 ng/mL, the following day tacrolimus dose was halved but tacrolimus serum levels continued to increase to 45.8 ng/mL, on day 23 tacrolimus was withheld. The patient began to show signs of toxicity (diarrhoea, body stiffness, tremors, altered mental status) and transferred to an intensive care unit. A third urine toxicology screen was done on day 28, this was negative for THC. Tacrolimus was withheld until day 31, with blood serum levels taken on a daily basis, tacrolimus was restarted when serum levels reached were in the therapeutic range.

Comment:
Without THC and CBD levels being recorded the quality and dose administered in this patient is unable to be assessed. Both THC and CBD are metabolised by CYP450 enzymes, there is limited comparative data on how each cannabinoid can affect the drug metabolism pathway. However, this case report does highlight the risk of DDI associated with concurrent use of CBD and a calcineurin inhibitor in transplant patients.

3.3 [redacted]

3.3.1 [redacted]

[redacted]

- [redacted]

[redacted]

3.3.2 [redacted]

[redacted]

- [redacted]

[redacted].

3.4 [redacted]

[redacted]

[redacted]

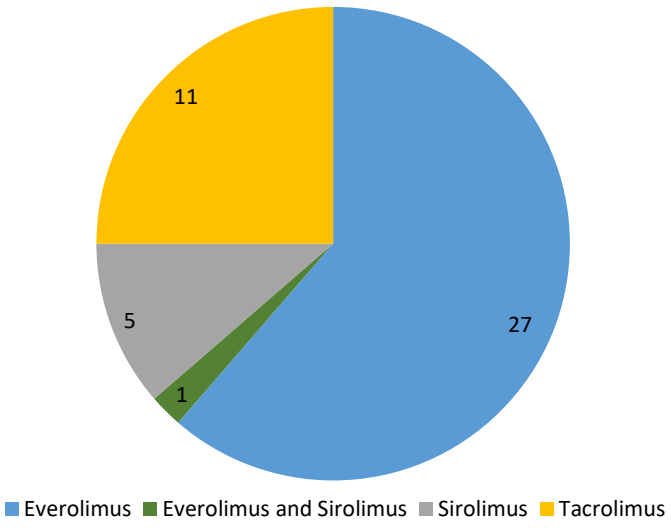
[redacted]

[redacted]

3.5 FAERS

A search of the FDA FAERS database up to 1 August 2022 found 342 cases of 'drug interaction' where CBD is listed as a suspect ingredient. Of these, 44 cases co-reported an mTOR and/or calcineurin inhibitor as a suspect or concomitant medicine (Figure 12). Out of the mTOR and calcineurin reports, everolimus had the highest number of reports (27). There were no reports for ciclosporin. Figure 12highlights these cases by concomitant drugs listed.

Figure 12: Number of cases where 'drug interaction' was reported with CBD and mTOR or calcineurin inhibitor, up to 1 August 2022.



Source: Food and Drug Agency. 2022. *FAERS database.* URL: https://open.fda.gov/data/faers/ (accessed 1 August 2022)

Comments:
The number of FAERS reports where CBD was a listed medicine for any ADR increased sharply in 2019 (3,064 reports) compared with the previous reporting years 2014-2018 (range: 1-58 reports). Since 2018, 39 states have legalised medicinal cannabis and 18 states have legalised recreational cannabis use. Increased availability and use may result in a higher number of ADR reports. However, it's possible people do not report suspected cannabis related ADRs in places where its use is illegal.

3.6 CARM data

A search of the CARM database up to 29 July 2022 found 23 reports where CBD is listed as a suspect medicine. There are four reports which represent a potential drug interaction (not all the reports are coded with drug-drug interaction but have been included based on a plausible mechanism) these are summarised below (Table 2). None of these reports list an mTOR or calcineurin inhibitor as a suspect, concomitant or interacting medicine.

Table 2: Summary of CARM reports for CBD and drug interactions, up to 29 July 2022

CARM ID #	Patient details, date of report	Medicine(s)	Description
141114	23y-o M May 2021	Paroxetine (suspect) Cannabidiol (suspect)	[redacted] drug interaction, night sweats, irritability, dizziness [redacted]
142810	49y-o F Dec 2021	Cannabidiol (suspect) Sertraline Risperidone	Nausea, diarrhoea, dry mouth, drunkenness feeling, paranoid reaction. [redacted]
140337	76y-o F April 2021	Cannabidiol (suspect) Warfarin (suspect)	Rectal bleeding, INR increase, drug interaction [redacted]
134798	28y-o F Oct 2021	Ondansetron (suspect) Cannabis oral (suspect) Morphine sulphate	Dystonia [redacted]

Comments:
DDIs resulting in an ADR are voluntary reported to CARM. It's possible DDIs occur but are not clinically significant and do not lead to an ADR hence there is no need to make a report. It's also possible that there is a lack of awareness around CBD/cannabis and DDIs- people may not contribute their ADR to CBD use. Lastly, CBD and cannabis products may be obtained illegally, people may not feel comfortable disclosing use to their healthcare professional and therefore it may not be listed as a substance on the CARM report.

4 DISCUSSION AND CONCLUSIONS

mTOR and calcineurin inhibitors are immunosuppressant agents commonly used in organ transplant medicine regimens. Variability in drug levels is concerning and is associated with negative treatment outcomes. The PRAC recently reviewed the risk of drug interaction between cannabidiol and mTOR and/or calcineurin inhibitor leading to serum level increase and toxicity. In March 2022, the PRAC recommended updates to the SmPC to include the DDI. Overall, there is very little information on whether there is a clinically significant interaction between CBD and all systemic mTOR and calcineurin inhibitors. The mechanism of which CBD contributes to DDIs is via enzymes and transporters involved in drug metabolism (CYP450 enzymes and P-gp).

Several pharmacokinetic studies conducted in humans report interactions between CBD and various antiepileptic drugs (including clobazam, N-desmethylclobazam, and valproate). A recent study by Ebrahimi-Fakhari et al suggests CBD may cause clinically significant interactions with mTOR and calcineurin inhibitors [26]. A small number of case reports are available in the literature where authors describe increased drug levels of an mTOR or calcineurin inhibitor following use of cannabis products. These case reports often lack information but highlight the possible risk of a DDI. The authors of these report suggest the need for ongoing monitoring and potential dose adjustments of mTOR or calcineurin inhibitors. No reports were identified in the literature for a DDI between CBD and concomitant use with ciclosporin. All studies recommend additional formal clinical trials to investigate the clinical significance and safety of a potential DDIs between CBD and mTOR and calcineurin inhibitors.

In the New Zealand context, there are currently 23 CARM reports where CBD is listed, of which four represent a potential drug interaction, none of these cases list an mTOR or calcineurin inhibitor as a suspect, concurrent or interacting medicine. Based on the biologically plausible mechanism of which CBD can contribute to DDIs it is possible that ADRs occur but are not reported. The Medicinal Cannabis Scheme seeks to increase access to medicinal cannabis products. There is a risk that the incidence of potentially clinically significant interactions between CBD and other medicines will increase. Healthcare professionals and consumers may not be aware of a potential interaction as most medicinal cannabis products available in New Zealand do not have published data sheets, and the information in clinical references sources is inconsistent.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the available evidence supports a clinically significant drug-drug interaction between cannabidiol and systemic mTOR and calcineurin inhibitors?
- If so, does the wording in the data sheets for all products (mTOR, calcineurin inhibitor, and cannabidiol) need to be updated?
- Does this topic need further communication other than MARC's remarks in Prescriber Update?

6 ANNEXES

Annex 1: Stockley's Drug Interactions: Summary of Cannabidiol drug interactions

Annex 2: Summary of PRAC wording recommendations for mTOR and calcineurin inhibitors

Annex 3: Ebrahimi-Fakhari et al: Cannabidiol Elevates Mechanistic Target of Rapamycin Inhibitor Levels in Patients With Tuberous Sclerosis Complex

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