Medicines Adverse Reactions Committee

Meeting date	**6 December 2018**	Agenda item	3.2.2
Title	**Viekira Pak/Viekira Pak-RBV and psychiatric changes**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Brand name	**Active ingredient(s)**		**Sponsors**
Viekira Pak	ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets co-packaged with dasabuvir 250 mg tablets		AbbVie Ltd
Viekira Pak-RBV	ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets co-packaged with dasabuvir 250 mg tablets and ribavirin 200, 400 or 600 mg tablets		AbbVie Ltd
Funding	Viekira Pak/Viekira Pak-RBV funded in the community and through hospitals since 1 July 2016, through PHARMAC's direct distribution supply.		
Previous MARC meetings	Viekira Pak/Viekira Pak-RBV was discussed previously at the following meeting: – 166th Meeting — 8 September 2016 ○ Hepatitis B Reactivation with Direct-Acting Antivirals for Hepatitis C.		
Prescriber Update	Safe prescribing of direct-acting antivirals for treatment of hepatitis C — it's complicated. *Prescriber Update* 37(4): 50-1. URL: www.medsafe.govt.nz/profs/PUArticles/December%202016/AntiviralsForTreatmentHepatitisC.htm		
Schedule	Prescription medicine		
Usage data	[redacted]		
Advice sought	**The Committee is asked to advise whether:** – There is sufficient evidence for an association between Viekira Pak/Viekira Pak-RBV and severe psychiatric changes, and if so: ○ is a data sheet update required ○ does this topic require further communication, other than MARC's remarks in *Prescriber Update.*		

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1.0 PURPOSE

As part of routine pharmacovigilance monitoring, Medsafe identified possible safety signals of hallucination associated with ribavirin (CARM ID 127069) and psychotic symptoms associated with Viekira Pak-RBV (127641). Further investigation of these case reports revealed that both patients were taking Viekira Pak-RBV, of which, ribavirin is an active component.

Hallucination or psychotic disorder are not listed as adverse events in the Viekira Pak-RBV data sheet. Medsafe asked the sponsor, AbbVie, to provide a company review of psychiatric changes (in particular, hallucinations and psychosis/psychotic disorders) associated with the use of Viekira Pak/Viekira Pak-RBV (Annex 1).

The data sheet for ribavirin (Copegus, Roche) includes information relating to psychotic disorder and hallucination which is prefaced as "uncommon to rare" in patients receiving peginterferon alfa-2a/Copegus combination or peginterferon alfa-2a monotherapy during clinical trials. Section 4.8 of the Viekira Pak-RBV datasheet was recently updated to include the following statement:

> *Please also refer to the currently approved datasheet for Ribavirin Tablets (eg, Copegus®) for further information and a list of ribavirin-associated adverse reactions.*

Medsafe also asked Roche to provide the data behind these listed adverse events for Copegus, and any other information that may be useful (Annex 2).

This paper seeks advice on whether there is sufficient evidence for an association between Viekira Pak/Viekira Pak-RBV and psychotic disorder and/or hallucinations, and if so, if any regulatory activity is required.

2.0 BACKGROUND

2.1 Viekira Pak/Viekira Pak-RBV

Viekira Pak and Viekira Pak-RBV are direct-acting antivirals (DAAs), used for the treatment of chronic hepatitis C infection. DAAs can be used without interferons, which are less well tolerated. Until recently, interferons were the only option for treatment of hepatitis C.

- Viekira Pak is fixed-dose combination tablets of ombitasvir/paritaprevir/ritonavir, co-packaged with dasabuvir tablets.
- Viekira Pak-RBV is fixed-dose combination tablets of ombitasvir/paritaprevir/ritonavir, co-packaged with dasabuvir tablets and ribavirin (RBV) tablets.

These products were approved in NZ on 6 August 2015. See section 2.4.1 for prescribing information.

Comment

The DAA components are ombitasvir, paritaprevir and dasabuvir; this presentation is commonly referred to as a 3-DAA regimen. Ritonavir and ribavirin are not DAAs.

2.1.1 Mechanism of action

DAAs work by blocking the action of proteins in HCV which are essential for viral reproduction. The specific mechanism of action for each DAA in Viekira Pak/Viekira Pak-RBV is listed below, and their specific targets are shown in Figure 1.

Paritaprevir: An inhibitor of HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV-encoded polyproteins (into mature forms of the NS3, NS4A, NS4B, NS5A and NS5B proteins) and is essential for viral replication [1].

Ombitasvir: An inhibitor of HCV NS5A, which is necessary for viral replication [1].

Dasabuvir: A non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene [1].

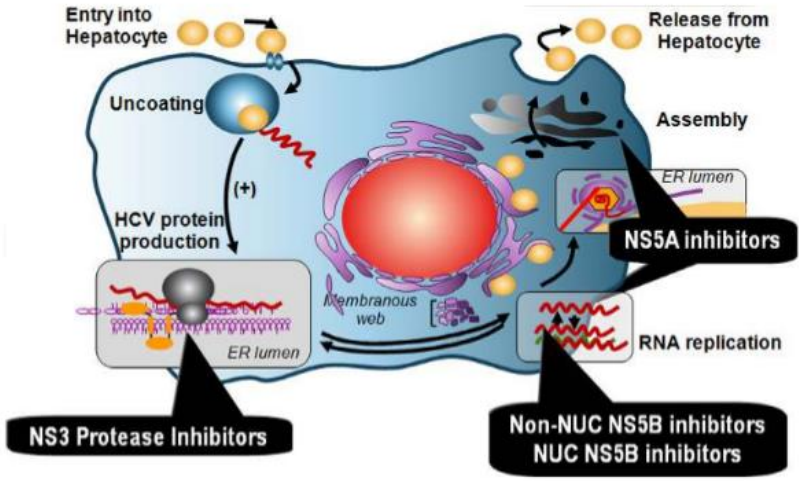

Figure 1: Specific targets of DAAs [2]

Ritonavir: Not a DAA and not active against HCV [1]. Ritonavir is a pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (ie, area under the curve).

Ribavirin: A synthetic nucleoside analogue and not a DAA [1]. The mechanism by which ribavirin exerts its effects against HCV is unknown. Oral formulations of ribavirin monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that ribavirin monotherapy had no effect on eliminating hepatitis virus (HCV-RNA) or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up. Monotherapy with ribavirin is not recommended.

2.1.2 Funding

Viekira Pak/Viekira Pak-RBV has been fully funded by PHARMAC since 1 July 2016 for patients with hepatitis C genotypes 1a and 1b, see section 2.2.4.1 for details.

Ledipasvir/sofosbuvir (Harvoni; another DAA) ±RBV, has also been funded since 1 July 2016 for patients with any hepatitis C genotype and with advanced disease.

2.1.3 Usage Data

[redacted]

[redacted]

2.1.3.2 New Zealand

[redacted]

2.2 Hepatitis C

2.2.1 Background

Hepatitis C virus (HCV) can cause both acute and chronic hepatitis infection ranging in severity from a mild illness lasting a few weeks to a serious lifelong illness. Acute HCV infection is usually asymptomatic and is only very rarely associated with life-threatening disease [4].

HCV is a bloodborne virus. It is most commonly transmitted through:

- unsafe injection practices
- inadequate sterilisation of medical equipment
- transfusion of unscreened blood and blood products [5].

HCV can also be transmitted sexually and can be passed from an infected mother to her baby [5]. However, these modes of transmission are much less common.

The incubation period for hepatitis C is 2 weeks to 6 months [5]. Following initial infection, approximately 80% of people do not exhibit any symptoms [5]. Because of this, few people are diagnosed during the acute phase. In those people who go on to develop chronic HCV infection, the infection is also often undiagnosed because the infection remains asymptomatic until decades after infection when symptoms develop secondary to serious liver damage [5].

About 15–45% of infected persons spontaneously clear the virus within 6 months of infection without any treatment [4]. The remaining 55–85% of persons will develop chronic HCV infection [4]. Of those with chronic HCV infection, the risk of cirrhosis of the liver is between 15–30% within 20 years [4].

The spectrum of disease in persons infected with HCV extends from mild fibrosis to cirrhosis and hepatocellular carcinoma (HCC) [4]. Compensated cirrhosis may progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening [4]. HCC may also occur at a rate of 2–4% per year in persons with cirrhosis [4]. The diagnosis of decompensated liver disease is based on both clinical examination and laboratory monitoring [4]. Therefore, a careful medical examination of patients must be made prior to commencing therapy [4].

Staging of HCV infection is important as it identifies patients with advanced disease, a group that requires enhanced monitoring and prioritisation for treatment before the onset of decompensated cirrhosis [4].

Disease associated with HCV infection is not confined to the liver [4]. Extrahepatic manifestations of HCV include cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjogren syndrome, insulin resistance, type 2 diabetes, and skin disorders such as porphyria cutanea tarda and lichen planus [4]. Persons with chronic HCV infection are more likely to develop cognitive dysfunction, fatigue and depression [4]. These outcomes may be associated with replication of the virus in the brain; however, the causal link between these manifestations and chronic HCV infection is not certain. See section 2.3 below.

2.2.2 Epidemiology

2.2.2.1 Global

The global prevalence of viraemic HCV was estimated to be 1.0% (uncertainty interval 0.8–1.1) in 2015, corresponding to 71.1 million infections (62.5–79.4) [6]. This is much lower than previous global estimates which used older and higher prevalence estimates for China and India; more recent studies show a much lower infection rate in these countries [6].

Modelling estimates suggest there were 1.75 million new HCV infections in 2015 (global incidence rate: 23.7 per 100,000) [7]. Most of these new infections were due to unsafe health-care procedures and injection drug use [7].

A significant number of those who are chronically infected with HCV will develop liver cirrhosis or liver cancer. In 2015, approximately 400,000 people globally died from HCV-related liver cirrhosis or liver cancer [7].

2.2.2.2 New Zealand

There are more than 50,000 people living with HCV in NZ, although it is estimated that only half are currently diagnosed [8]. There are approximately 1000 new cases each year. Hepatitis C is the leading cause of liver transplantation in New Zealand [8].

It is assumed that the epidemiology in NZ follows that of Australia, where chronic, as well as incident, HCV is a notifiable disease (270,000 identified cases, prevalence 1.28%) [9, 10]. However the epidemiologic data on HCV in NZ is poor because only acute infection is notifiable. A recent NZ study estimated that 4.01% (95% CI: 2.6–5.8%) of asymptomatic 40–59 years old adults living in Dunedin city are infected with HCV [9].

Acute hepatitis C notifications by year from 1997–2016 are shown in Figure 2 and exposure to risk factors are summarised in Table 3. Although the HCV-infected population has been relatively stable since 2000, the numbers with cirrhosis have doubled over the last decade because of an aging cohort effect and very low rate of treatment uptake [10]. Adults in the 40–49 (1.8 per 100,000) and 30–39 years (1.7 per 100,000) age groups had the highest notification rates in 2016 [11]. In 2015, there were 356 new registrations for liver cancer (of any origin) with a rate of 5.0 per 100,000 [12].

Table 3: Exposure to risk factors associated with acute hepatitis C in NZ, 2016 [11]

Risk factor	Yes	No	Unknown	Percentage (%) [a]
History of injecting drug use	20	6	4	76.9
Body piercing/tattooing in the last 12 months	5	15	10	25.0
Sexual contact with confirmed case or carrier	4	12	14	25.0
Household contact with confirmed case or carrier	3	16	11	15.8
Occupational exposure to blood	3	21	6	12.5

[a] Percentage refers to the number of cases that answered "yes" out of the total number of cases for which this information was known. Some cases had more than one risk factor recorded.

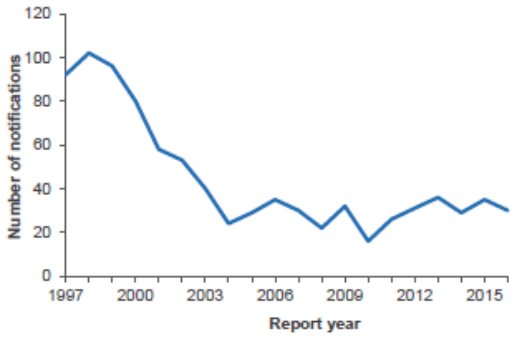

Figure 2: Acute hepatitis C notifications in NZ by year, 1997–2016 [11]

Comment

In NZ, only acute hepatitis C is a notifiable disease. However, according to the WHO, few people are diagnosed during the acute phase because 80% of people do not exhibit any symptoms. The Ministry of Health estimates that only half are currently diagnosed. Therefore, the full picture of chronic hepatitis C in NZ is not known.

2.2.3 Genotypes

HCV is a small positive-stranded RNA-enveloped virus. It has a highly variable genome which has been classified into six distinct genotypic groups [4]. Current DAA treatments are significantly more effective on certain genotypes than others so it is important to know a person's genotype prior to initiating treatment [4].

The distribution of HCV genotypes and subgenotypes varies substantially in different parts of the world (Figure 3). At the global level, genotype 1 accounts for 44% of all infections, followed by genotypes 3 (25%) and 4 (15%) [6].

The prevalent HCV infected population in NZ was estimated at 50,000 individuals in 2013 [10]. The genotype distribution of the prevalent population was based on the distribution in more than 2000 individual results from a reference laboratory: G1 (56%), G3 (35%) and G2 (8%) [10]. It is possible for a person to be infected with more than 1 genotype.

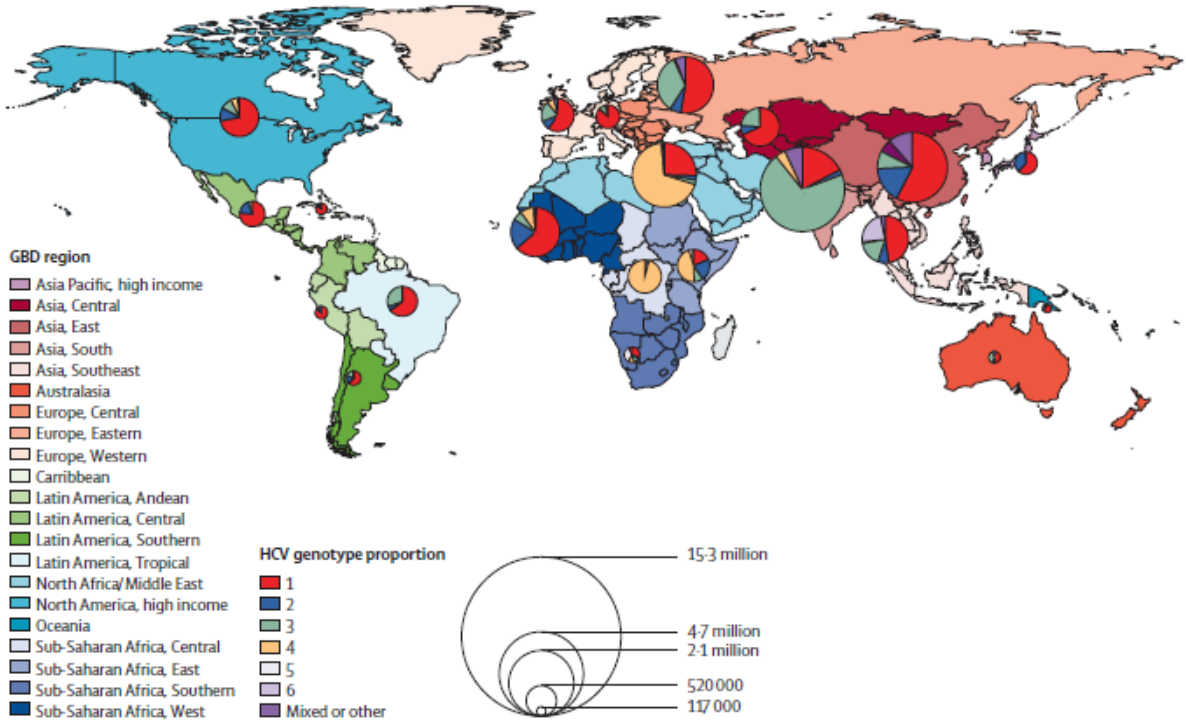

Figure 3: Global distribution of HCV genotypes and total infected by Global Burden of Disease Region, 2015 [6]

Comment

The prevalent HCV infected population in NZ was estimated at 50,000 individuals in 2013. As in the rest of the world, most have HCV genotype 1 or 3.

2.2.4 Treatment and prevention

Hepatitis C does not always require treatment as the immune response will clear the infection in some people, and some people with chronic infection do not develop liver damage [5]. The goal of hepatitis C treatment is cure or SVR (sustained virological response), defined as undetectable plasma HCV RNA at least 12 weeks after treatment has ceased [13]. SVR is associated with multiple clinical benefits, including improvement in quality of life, loss of infectivity, regression of liver fibrosis and cirrhosis, a reduction in the risk of liver failure and HCC, and a reduction in the risk of liver-related and all-cause mortality [13]. The cure rate depends on several factors including the strain of the virus and the type of treatment given, but can be as high as 95% with DAA therapy [5].

Until recently, hepatitis C treatment was based on therapy with pegylated interferon and ribavirin which required weekly injections for 48 weeks, cured approximately half of treated patients with frequent and sometimes life-threatening adverse reactions [4]. The WHO now recommends that all patients with hepatitis C be treated with DAA-based regimens except for a few specific groups of people in whom interferon-based regimens can still be used (pegylated interferon + sofosbuvir and ribavirin is still recommended as an alternative treatment option for patients with HCV genotype 3 infection with cirrhosis and patients with genotypes 5 and 6 infection with and without cirrhosis) [4]. Likewise, the NZ Society of Gastroenterology HCV Treatment Guidelines recommends use of DAAs rather than interferon-based therapy [14] (Annex 3).

2.2.4.1 Treatment in NZ

While several DAA treatments are approved in NZ, only Viekira Pak/Viekira Pak-RBV and ledipasvir/sofosbuvir (Harvoni) are funded. Viekira Pak/Viekira Pak-RBV are indicated for genotypes 1a and 1b, with no funding restrictions [15]. Harvoni is indicated for genotypes 1, 4, 5 or 6, and funding is currently restricted to patients with any genotype with severe liver disease. Therefore the majority of people with genotype 2–6 have no funded DAA treatment option [15]. These people, if they choose to be on treatment, currently use interferon-based therapies which are less effective and can be poorly tolerated [15].

In August 2017, the Pharmacology and Therapeutics Advisory Committee (PTAC) recommended that glecaprevir/pibrentasvir (Maviret) be funded for the treatment of chronic hepatitis C in adults, conditional on registration with Medsafe and publication of clinical trial data in peer-reviewed journals [16]. Maviret is a pangenotypic DAA treatment indicated for use in patients with chronic HCV [17]. PTAC considered that in comparison with Viekira Pak/Viekira Pak-RBV, Maviret has better efficacy, no requirement for ribavirin, which reduces the number of side-effects and complexity of treatment, significantly fewer drug-drug interactions and has a reduced treatment duration [16]. The Committee considered that these benefits, along with no requirement for pre-treatment genotype testing, should make prescribing by general practitioners straight forward [15].

In July 2018, PHARMAC sought feedback on a proposal to fund Maviret [15]. If funded, Maviret would replace Viekira Pak/Viekira Pak-RBV. As at 24 October 2018, this proposal was still being reviewed by PHARMAC and the product will not be listed before the end of 2018 [18].

Comment

Glecaprevir/pibrentsavir (Maviret) is indicated for all HCV genotypes. If glecaprevir/pibrentsavir is funded it will replace Viekira Pak/Viekira Pak-RBV. AbbVie is the sponsor for all of these products. It is unclear at this stage whether AbbVie will withdraw Viekira Pak/Viekira Pak-RBV from the market if Maviret is funded.

2.2.4.2 Prevention

There is currently no vaccine for hepatitis C; however research in this area is ongoing. Prevention of HCV infection depends on reducing the risk of exposure to the virus in healthcare settings and in higher risk populations. There is currently no nationally-funded HCV screening programme to identify all people in NZ with HCV, although this has been proposed.

2.3 Psychosis and psychotic disorders

2.3.1 Background

It is estimated that 13–23 percent of people experience psychotic symptoms at some point in their lifetime, and 1–4 percent will meet criteria for a psychotic disorder [19].

Psychosis is a condition of the mind broadly defined as a loss of contact with reality [19], where the patient may experience delusions, hallucinations, disorganised thinking (speech), grossly disorganised or abnormal motor behaviour (including catatonia) or negative symptoms [20].

- Delusions are defined as strongly held false beliefs that are not typical of the patient's cultural or religious background [19]. They can be categorised as bizarre or non-bizarre based on their plausibility (eg, a belief that family members have been replaced by body-doubles is bizarre and a belief that a spouse is having an affair is non-bizarre) [19].
- Hallucinations can be defined as wakeful sensory experiences of content that is not actually present [19]. While hallucinations can occur in any of the five sensory modalities, auditory hallucinations are the most common, followed by visual, tactile, olfactory, and gustatory hallucinations [19].
- Disorganised thinking is typically inferred from the individual's speech [20]. While disorganized speech is a frequently observed symptom in psychosis, it is nonspecific and can also be present in delirium or other neurological or cognitive disorders [19].
- Grossly disorganised or abnormal motor behaviour may manifest itself in a variety of ways, ranging from childlike silliness to unpredictable agitation [20].
- Negative symptoms account for a significant proportion of the morbidity associated with schizophrenia but are less prominent in other psychotic disorders [20]. Diminished emotional expression and avolition (a decrease in motivated self-initiated purposeful activities) are two negative symptoms particularly prominent in schizophrenia [20].

Psychotic symptoms can be associated with a wide variety of primary psychiatric illnesses and medical illnesses or be substance- or medication-induced [19]. Clinical features of the psychosis are not specific to a particular diagnosis, but can provide evidence suggestive of primary psychiatric versus medical aetiologies [19] – see Table 4.

Table 4: Clinical features of psychosis associated with primary psychiatric disorders and medical conditions [19]

Clinical feature	Associated with primary psychiatric (psychotic) disorders	Associated with medical conditions
Family history	Often present	Variably present
Onset	Insidious	Acute
Age at onset	Teens to mid-thirties	Forties or older
Health care setting for first presentation	Variable	General medical or intensive care settings
Hallucinations	Auditory	Non-auditory (visual, tactile, olfactory)

2.3.2 Primary psychiatric illnesses

Psychiatric illnesses are generally classified by diagnostic criteria established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the International Classification of Diseases (ICD, World Health Organization) [19]. Primary psychiatric illnesses that may present with psychotic symptoms include schizophrenia, delusional disorder, brief psychotic disorder, major depressive disorder with psychotic features and bipolar disorder with psychotic features.

2.3.3 Psychoses associated with medical or neurological conditions

A large number of medical illnesses can be accompanied by psychotic symptoms, including endocrine disorders, hepatic and renal disease, infectious disease, neurological disorders and vitamin B12 deficiency [19].

2.3.3.1 Hepatitis C virus

Many individuals with HCV report cognitive symptoms, which are often associated with objective evidence of neurocognitive impairment as well as psychiatric syndromes [21]. These sequelae occur commonly, are often present prior to the development of clinically significant liver disease, and may be exacerbated by advanced liver disease and other common comorbidities [21].

The hepatitis C virus primarily infects hepatocytes but also causes extrahepatic disease, impacting numerous organ systems (eg, endocrine, lymphatic, renal) including central nervous system (CNS) structure and function [21]. Brain imaging has shown increased neuroinflammation in those with HCV viremia versus healthy controls [22]. Hepatitis C viremia is thought to induce neuroinflammation through penetration and replication in the central nervous system, which results in altered metabolism and downstream neurotoxicity [22, 23]. These disturbances are of sufficient magnitude to increase disease burden and impact patient management [21].

Up to 50% of patients with untreated chronic HCV may suffer from psychiatric illness when substance abuse and dependence are excluded [24]. Lifetime rates of mood, anxiety and personality disorders in untreated HCV-infected patients have each ranged from approximately 20% to 40% [24]. A recent observational study of 1,600 patients with chronic HCV in the US found that 18% of the cohort reported a past history of inpatient psychiatric hospitalisations, a proxy for severe psychopathology [25].

2.3.4 Substance/medication-induced psychotic disorders

Many prescription medications as well as illicit substances can induce transient psychotic symptoms. The DSM-5 [20] defines “substance/medication-induced psychotic disorder” as having the presence of delusions and/or hallucinations during or soon after intoxication, withdrawal, or exposure to a substance, with the disturbance not being better explained by another type of psychotic disorder [19]. The disturbance cannot “occur exclusively during the course of a delirium” and must cause significant distress or impairment in function [19]. Table 5 lists major substances, medications, and toxins that can cause transient psychoses.

Table 5: Substances and medications with capacity to induce psychosis [19]

Substance or medication	Examples
Alcohol and sedatives/hypnotics	Alcohol (intoxication or withdrawal), barbiturates, benzodiazepines (particularly withdrawal)
Anabolic steroids	Testosterone, methyltestosterone
Analgesics	Meperidine, pentazocine, indomethacin
Anticholinergics	Atropine, scopolamine
Antidepressants	Bupropion, others if triggering a manic switch
Antiepileptics	Zonisamide, other anticonvulsants at high doses
Antimalarial	Mefloquine, chloroquine
Anti-parkinsonian	Levodopa, selegiline, amantadine, pramipexole, bromocriptine
Antivirals	Abacavir, efavirenz, nevirapine, acyclovir
Cannabinoids	Marijuana, synthetic cannabinoids (ie, "spice"), dronabinol
Cardiovascular	Digoxin, disopyramide, propafenone, quinidine
Corticosteroids	Prednisone, dexamethasone, etc
Hallucinogens	LSD, PCP (phencyclidine), ketamine, psilocybin-containing mushrooms, mescaline, synthetic "designer drugs", salvia divinorum
Inhalants	Toluene, butane, gasoline
Interferons	Interferon alfa-2a/2b
Over-the-counter (OTC)	Dextromethorphan, diphenhydramine, some decongestants

Substance or medication	Examples
Stimulants	Cocaine, amphetamine/methamphetamine, methylphenidate, certain diet pills, "bath salts" (MDPV, mephedrone), MDMA/ecstasy
Toxins	Carbon monoxide, organophosphates, heavy metals (eg, arsenic, manganese, mercury, thallium)

2.3.4.1 HCV treatments

Interferons

Treatment with pegylated interferon-alpha (IFNα) therapy can induce numerous neuropsychiatric side effects, including depression and suicidal ideation, in approximately 25% to 30% of patients undergoing IFNα therapy for HCV [22, 24]. In addition, HCV-infected patients with pre-existing psychiatric disorders may experience an exacerbation of psychopathology secondary to IFNα [24].

Ribavirin

Ribavirin, often co-administered with IFN-α, is independently associated with depressive symptoms, though the exact rate is unclear [22].

DAAs

The extent of psychiatric effects attributed to DAA agents is unclear; but is noted to be less than IFNα-containing regimens [22]. Though data suggests that DAAs overall confer a minimal risk of psychiatric adverse effects compared to IFNα-based regimens, there is a lack of data specifically analysing neuropsychiatric complications of these agents [22]. Additionally, it is unclear whether DAA therapy may exacerbate mood symptoms in patients with prior psychiatric history [22]. Many DAA studies excluded those with recent psychiatric hospitalisation, suicide attempt, or psychiatric disability during clinical trials [22]. These studies did not use formal psycho-diagnostic tools to assess psychiatric adverse effects [22].

In addition, DAAs are known to interact and postulated to interact with a substantial list of medicines, including those metabolised or transported by [26]:

- CYP3A4
- Organic Anion Transporting Polypeptides (OATP) family and Organic Cation Transporter 1 (OCT1)
- Breast Cancer Resistance Protein (BCRP)
- P-glycoprotein (P-gp) in the intestine
- glucuronidation (UGT1A1)
- CYP2C19
- CYP1A2.

Negative consequences of such drug interactions may include viral breakthrough and development of resistance, sub-optimal disease/symptom management, or drug toxicity and possible non-adherence [24]. Given the high prevalence of psychiatric illness in HCV-infected patients, an understanding of drug interactions involving psychotropic medications is essential to the clinical care of patients treated for HCV [24].

See section 2.4.1.2 for information about potential drug interactions with Viekira Pak/Viekira Pak-RBV.

Comment

Psychotic symptoms can be associated with a wide variety of primary psychiatric illnesses and medical illnesses or be substance- or medication-induced. Therefore, there is a high potential for confounding when trying to assess the relationship between Viekira Pak/Viekira Pak-RBV and psychiatric changes.

2.4 Data sheets

Relevant sections of the Viekira Pak/Viekira Pak-RBV data sheets are summarised below. Information from other RBV-containing data sheets (Copegus, [redacted] Pegasys RBV) is also included for comparison.

2.4.1 Viekira Pak & Viekira Pak-RBV [1, 27]

2.4.1.1 Indications and dosing

Viekira Pak/Viekira Pak-RBV are indicated for the treatment of genotype 1 chronic hepatitis C infection, including patients with compensated cirrhosis, HIV-1 co-infection, and liver transplant recipients. Duration of therapy and addition of ribavirin are dependent on patient population – see Table 6.

The recommended oral dose of Viekira Pak is two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening). The ribavirin tablets contain 200 mg of ribavirin. The recommended daily dose of ribavirin depends on patient's bodyweight (<75 kg = 1000 mg and ≥75 kg = 1200 mg), and should be taken with food in two divided doses (morning and evening).

Table 6: Viekira Pak/Viekira Pak-RBV treatment regimen and duration by patient population [1]

Patient Population	Treatment	Duration	Ribavirin Dosage
HCV Genotype 1b, with or without cirrhosis	VIEKIRA PAK	12 weeks 8 weeks may be considered in previously untreated patients without advanced fibrosis or cirrhosis (see section 5.1 GARNET study)	No ribavirin required
HCV Genotype 1a, or unknown or mixed genotype 1, with or without cirrhosis	VIEKIRA PAK-RBV[a]	12 weeks[b]	Ribavirin to be taken in two divided doses (morning and evening) with food. Patients <75 kg = 1000 mg, taken as 2 x 200 mg tablets in the morning and 3 x 200 mg tablets in the evening[#]. Patients ≥75 kg = 1200 mg, taken as 3 x 200 mg tablets in the morning and 3 x 200 mg tablets in the evening[#].

[a] VIEKIRA PAK without ribavirin can be considered as a therapeutic option for treatment-naïve patients with HCV genotype 1a without cirrhosis (see section 5.1 Pharmacodynamic properties). Treatment decisions should be guided by an assessment of the potential benefits and risks and available alternative therapies for the individual patient.

[b] 24 weeks of VIEKIRA PAK–RBV are recommended for patients with HCV genotype 1a-with cirrhosis who have had a previous null response to pegIFN and ribavirin (see section 5.1 Pharmacodynamic properties).

[#] The starting dose of ribavirin should be reduced in patients with renal impairment (creatinine clearance ≤50 mL/min). Haemoglobin should be monitored in these patients and RBV dose reduced if necessary. Refer to the ribavirin prescribing information for further information.

Note: VIEKIRA PAK–RBV is recommended in patients with an unknown HCV genotype 1 subtype or with mixed genotype 1.

2.4.1.2 Contraindications and drug-drug interactions

Viekira Pak/Viekira Pak-RBV is contraindicated in patients with moderate to severe hepatic impairment.

Medicines that are sensitive CYP3A substrates, strong CYP2C8 inhibitors, or are moderate or strong inducers of CYP3A should not be co-administered with Viekira Pak/Viekira Pak-RBV. Table 7 lists the medicines which are contraindicated for use with Viekira Pak/Viekira Pak-RBV, those which are not recommended, medicines that require dose adjustments or monitoring and those that do not require dose adjustments.

Table 7: Recommendations for concomitant use of certain medications with Viekira Pak/Viekira Pak-RBV [1]

Medicines which are contraindicated for use with Viekira Pak/Viekira Pak-RBV	Medicines which are not recommended to be administered with Viekira Pak/Viekira Pak-RBV	Medicines for which dose adjustments and/or clinical monitoring are recommended when co-administered with Viekira Pak/Viekira Pak-RBV	Medicines which do not require dose adjustment when co-administered with Viekira Pak/Viekira Pak-RBV
• alfuzosin hydrochloride • astemizole, terfenadine • atorvastatin, lovastatin, simvastatin • blonanserin • carbamazepine, phenytoin, phenobarbital • cisapride • colchicine (patients with renal or hepatic impairment) • disopyramide • dronedarone • efavirenz • ergotamine, dihydroergotamine,	• atazanavir/ritonavir • everolimus • fluticasone • lopinavir/ritonavir • quetiapine • rilpivirine • sirolimus • tacrolimus	• alprazolam • amiodarone • amlodipine • atazanavira • bepridil • candesartan • carisoprodol • colchicine • cyclobenzaprine • cyclosporine • darunavir • darunavir/ritonavir • diazepam • digoxin • diltiazem • fluindione (INR monitoring recommended) • furosemide	• abacavir • buprenorphine • dolutegravir • duloxetine • emtricitabine • escitalopram • lamivudine • metformin • methadone • norethisterone (norethindrone) • paracetamol • raltegravir • sofosbuvir • sulfamethoxazole • tenofovir • trimethoprim • zolpidem

Medicines which are contraindicated for use with Viekira Pak/Viekira Pak-RBV	Medicines which are not recommended to be administered with Viekira Pak/Viekira Pak-RBV	Medicines for which dose adjustments and/or clinical monitoring are recommended when co-administered with Viekira Pak/Viekira Pak-RBV	Medicines which do not require dose adjustment when co-administered with Viekira Pak/Viekira Pak-RBV
ergonovine, methylergonovine • ethinyloestradiol-containing medications, eg combined oral contraceptives • fusidic acid • gemfibrozil • lurasidone • oral midazolam, triazolam • pimozide • ranolazine • rifampicin • salmeterol • St. John's wort • sildenafil (when used for the treatment of pulmonary arterial hypertension)		• hydrocodone • ketoconazole • lidocaine (systemic) • losartan • nifedipine • omeprazole • pravastatin • propafenone • quinidine • rosuvastatin • valsartan • verapamil • vitamin K antagonists (INR monitoring recommended) • voriconazole • warfarin (INR monitoring recommended)	

Ribavirin is contraindicated for pregnant women, men whose female partners are pregnant, patients with a history of severe pre-existing cardiac disease, with severe hepatic dysfunction or decompensated liver disease, with haemoglobinopathies.

2.4.1.3 Adverse events

Section 4.8 Undesirable effects states:

- Because clinical trials are conducted under widely varying conditions, rates of adverse reactions observed in clinical trials of VIEKIRA PAK/VIEKIRA PAK-RBV cannot be directly compared to rates in the clinical trials of another medicine and may not reflect the rates observed in practice.
- Please also refer to the currently approved datasheet for Ribavirin Tablets (e.g. COPEGUS) for further information and a list of ribavirin-associated adverse reactions.

Comment

The second bullet point above was added to the data sheet in August 2018, as described previously (see section 1.0).

Note that the ribavirin tablets included with AbbVie's Viekira Pak-RBV are not approved or available in New Zealand as a separate medicine, and so there is no currently approved data sheet. The Copegus ribavirin tablets referred to above are a Roche product (see section 2.4.2 below).

[redacted]

Adverse events in clinical trials

In pooled data from phase 2 and 3 trials (> 2,600 patients) the most commonly reported adverse reactions were:

- Viekira Pak-RBV:
  - fatigue and nausea (> 20% of patients).
  - 7.7% (158/2,044) of patients had ribavirin dose reductions due to adverse events.
  - The safety profile of VIEKIRA PAK-RBV in patients with cirrhosis was similar to that of patients without cirrhosis.
- Viekira Pak:
  - pruritus was the only identified adverse reaction.

The safety profile of Viekira Pak-RBV was consistent with the known safety profile of ribavirin.

In the psychiatric disorders system organ class, sleep disorder occurred with a frequency 2–5% higher among patients receiving Viekira Pak-RBV compared to patients receiving placebo.

Post-marketing adverse reactions

- Immune System Disorders: Anaphylactic reactions and other hypersensitivity reactions (including tongue and lip swelling).
- Hepatobiliary Disorders: Hepatic decompensation and hepatic failure.
- Skin and Subcutaneous Tissue Disorders: Erythema multiforme.

Comment

Sleep disorder is the only adverse event listed in the Psychiatric disorders system organ class in the Viekira Pak-RBV data sheets.

2.4.2 Copegus (ribavirin) [28]

2.4.2.1 Indications and dosing

RBV is indicated, in combination with peginterferon alfa-2a or interferon alfa-2a, for the treatment of chronic hepatitis C (CHC) in adult patients and who are positive for serum HCV RNA, including patients with compensated cirrhosis. The dose and duration of RBV treatment is based on the patient's HCV genotype and body weight and whether RBV is used in combination with peginterferon or interferon (800–1200 mg per day, and 24–72 weeks of treatment).

2.4.2.2 Adverse events

Adverse events reported in patients receiving RBV in combination with alpha interferon are essentially the same as those reported for RBV in combination with peginterferon alfa-2a. Of the psychiatric disorders system organ class, insomnia, irritability and depression were the most commonly reported adverse events in clinical trials (Table 8).

Table 8: Psychiatric adverse reactions reported in clinical trials, RBV + peginterferon (>10% incidence in any treatment group) [28]

	HCV (treatment naïve)		HIV – HCV (treatment naïve)	HCV (prior treatment non-responder)
	Copegus 800 mg + Peginterferon alfa-2a 180 mcg (NV 15492) 24 weeks *n* = 207	Copegus 1000 or 1200 mg + Peginterferon alfa-2a 180 mcg (NV 15801 + NV 15942) 48 weeks *n* = 887	Copegus 800 mg + Peginterferon alfa-2a 180 mcg (NR 15961) 48 weeks *n* = 288	Copegus 1000 or 1200 mg + Peginterferon alfa-2a 180 mcg (MV17150) 72 weeks *n* = 156
Body System	%	%	%	%
Psychiatric disorders				
Insomnia	30	32	19	29
Irritability	28	24	15	17
Depression	17	21	22	16
Concentration impairment	8	10	2	5

Neuropsychiatric effects reported in ≥1% but <10% on peginterferon alfa-2a/RBV combination or peginterferon alfa-2a monotherapy in HCV and HIV–HCV patients were: memory impairment, taste disturbance, paraesthesia, hypoesthesia, tremor, weakness, emotional disorders, mood alteration, nervousness, aggression, libido decreased, migraine, somnolence, hyperesthesia, nightmares, syncope, anxiety.

Uncommon to rare cases of suicide, substance overdose, psychotic disorder and hallucination have been reported in patients receiving peginterferon alfa-2a/Copegus combination or peginterferon alfa-2a monotherapy during clinical trials.

Comment

When ribavirin is used in combination with peginterferon alpha-2a for HCV treatment, the duration of treatment may be up to 6 times longer than when ribavirin is used with Viekira Pak.

Hallucinations and psychotic disorders have been reported in patients receiving ribavirin (Copegus) in combination with peginterferon alpha-2a or peginterferon alpha-2a monotherapy. See section 3.2.2 below for more information from Roche about this.

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2.4.4 Pegasys RBV (peginterferon alpha-2a + ribavirin)

2.4.4.1 Indications and dose

Pegasys RBV is indicated for the treatment of chronic hepatitis C (CHC) in non-cirrhotic patients and in cirrhotic patients with compensated liver disease [30]. Pegasys RBV is a combination therapy, containing Pegasys solution for injection (135/180 mcg peginterferon) and Copegus film-coated tablets (200 mg ribavirin). The duration of Pegasys RBV combination therapy, and the daily dose of Copegus, should be individualised based on the patient's viral genotype.

2.4.4.2 Warnings and precautions

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferons, including Pegasys RBV [30]. Depression, suicidal ideation, and suicidal attempt may occur in patients with and without previous psychiatric illness. Pegasys RBV should be used with caution in patients who report a history of depression, and physicians should monitor all patients for evidence of depression. Physicians should inform patients of the possible development of depression prior to initiation of Pegasys RBV, and patients should report any sign or symptom of depression immediately. In severe cases therapy should be stopped and psychiatric intervention sought (see Undesirable Effects).

Exercise caution and monitor for evidence of depression when administering Pegasys to paediatric patients with a prior history of or concurrent psychiatric disorders [30].

2.4.4.3 Adverse events

Table 10 shows the psychiatric adverse reactions occurring in ≥10% of patients who have received Pegasys, Pegasys RBV or interferon alfa-2b plus ribavirin in different indications.

Table 10: Psychiatric adverse reactions in clinical trial patients who have received Pegasys, Pegasys RBV or interferon alfa-2b plus ribavirin (≥10% Incidence in Any Treatment Group) [30]

	HCV (treatment naïve)				HIV-HCV (treatment naïve)	HCV non responder to prior peginterferon alfa-2b treatment
Body System	Pegasys 180 mcg 48 wk (NV15801 + monotherapy program)	Pegasys 180 mcg + 800 mg ribavirin 24 wk (NV15942)	Pegasys 180 mcg + 1000 mg or 1200 mg ribavirin 48 wk (NV15801 + NV15942)	IFN alfa-2b + 1000 mg or 1200 mg ribavirin 48 wk (NV15801)	Pegasys 180 mcg + 800 mg ribavirin 48 wk (NV15961)	Pegasys 180 mcg + 1000 mg or 1200 mg ribavirin 72 wk (MV17150)
	n = 827	*n* = 207	*n* = 887	*n* = 443	*n* = 288	*n* = 156
Psychiatric disorders						
Insomnia	20	30	32	37	19	29
Depression	18	17	21	28	22	16
Irritability	17	28	24	27	15	17
Concentration impairment	9	8	10	13	2	5
Anxiety	6	8	8	12	8	6

Neuropsychiatric disorders reported in ≥1% but <10% on Pegasys RBV combination or Pegasys monotherapy were: memory impairment, taste disturbance, paraesthesia, hypoaesthesia, tremor, weakness, emotional disorders, mood alteration, nervousness, aggression, libido decreased, migraine, somnolence, hyperaesthesia, nightmares, syncope, anxiety [30].

Uncommon to rare cases of suicide, substance overdose, psychotic disorder and hallucination have been reported in patients receiving Pegasys RBV or Pegasys monotherapy during clinical trials [30].

Comment

Hallucinations and psychotic disorders have been reported in patients receiving peginterferon alpha-2a in combination with ribavirin or peginterferon alpha-2a monotherapy and this is listed in the Pegasys RBV data sheet.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

One paper was retrieved.

3.1.1 Calleja et al, 2017 [31]

The authors performed a retrospective, non-interventional study evaluating the effectiveness and safety of two oral DAA combination regimens, ombitasvir/paritaprevir/ritonavir plus dasabuvir (OMV/PTV/r+DSV) and ledipasvir/sofosbuvir (LDV/SOF), in Spanish patients in real-world clinical practice.

Data from HCV genotype 1 patients treated with either OMV/PTV/r+DSV±ribavirin (RBV) (n=1567) or LDV/SOF±RBV (n=1758) in 35 centers across Spain between 1 April 2015 and 28 February 2016 were recorded in a large national database. No other inclusion or exclusion criteria were specified. Patient follow-up ranged from 24 to 36 weeks depending on-treatment duration. The decision to treat and the choice of treatment, including treatment duration and the use or not of concomitant RBV, was entirely at the discretion of the treating physician. Demographic, clinical and virological data were analysed. Details of serious adverse events (SAEs) were recorded. The two cohorts were not matched with respect to baseline characteristics and could not be compared directly. The safety results for OMV/PTV/r+DSV±RBV are described below.

Among the 1,567 patients treated with OMV/PTV/r+DSV±RBV, 33 patients (2.1%) discontinued treatment earlier than planned; 27 due to an adverse event (1.7%), 5 at patient request (0.3%), and 1 due to virologic breakthrough. Five out of the 33 patients with early treatment discontinuation achieved SVR12 (15.2%). Overall, 113 SAEs were reported in 84 patients (5.4%) (Table 11). The most commonly reported SAE was anaemia (1.5%), which occurred only in patients receiving RBV. Three patients (0.19%) experienced serious psychiatric disorders, although there was no additional information about the type of psychiatric disorder or whether the patients took concomitant RBV or not. The majority of SAEs were reported at week 4 (43%) and week 12 (41%) of treatment.

Incident hepatic decompensation occurred in 16 patients (0.9%); all patients had cirrhosis at baseline, ten with oesophageal varices. Decompensation was associated with a significantly higher baseline elastography (37.2 vs. 16.8; p <0.001), MELD score (11 vs. 8; p <0.001) and bilirubin level (1.7 vs. 0.98, p <0.001) and with a significantly lower albumin level at baseline (3.0 vs. 4.1, p <0.001). Eight deaths (0.5%) during treatment or follow-up were recorded, three of which were directly related to liver failure.

Age, sex, presence of cirrhosis (F4), baseline elastography values, Child–Pugh score, MELD score, a history of previous antiviral treatment, haemoglobin level, creatinine level, eGFR, bilirubin level, albumin level, platelet levels and international normalized ratio (INR) at baseline were all significantly related to the development of SAEs on univariate analysis (all p <0.05). Of these, patient age (p = 0.01), elastography score (p = 0.002) and MELD score (p = 0.001) remained significant on multivariate analysis.

The authors noted that in this study, reported rates of SAEs (5.5%) were similar to those reported in the pivotal clinical trials for OMV/PTV/r+ DSV, although the rate of SAEs in cirrhotic patients was slightly higher (8.1%) than in clinical trials (5.5%).

The authors conclude that in this large cohort of patients managed in the real-world setting in Spain, OMV/PTV/r+DSV and LDV/SOF achieved high rates of SVR12, comparable to those observed in randomised controlled trials, with similarly good safety profiles.

Table 11: Serious adverse events occurring during treatment or follow-up in ≥1 patient treated with ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavirin

Patients, n (%) (% patients with at least one event)/total patients	N = 1,567
Any serious adverse event	84 (5.4)
Adverse event leading to treatment discontinuation	27 (1.7)
Serious adverse events	
Anemia	24 (1.53)
Infection	8 (0.51)
Fatigue	3 (0.19)
Cardiovascular disease	6 (0.38)
Psychiatric disorders	3 (0.19)
Metabolic alteration	5 (0.32)
Neurologic disorders	0
Cutaneous disorders	11 (0.70)
Gastrointestinal disease	3 (0.19)
Renal failure	4 (0.26)
Neoplasia (not liver related)	3 (0.19)
Hepatic decompensation	8 (0.51)
Variceal bleeding	3 (0.19)
Hepatic encephalopathy	2 (0.13)
Ascites	3 (0.19)
Acute liver failure	1 (0.06)
Deaths	8 (0.5)
Non-liver-related deaths	
Severe cranioencephalic trauma	1 (0.06)
Hip fracture complications	1 (0.06)
Lung cancer	1 (0.06)
Acute leukemia	1 (0.06)
Acute pulmonary edema	1 (0.06)
Deaths directly related to liver failure	
Ascites	1 (0.06)
Acute liver failure	1 (0.06)
Lactic acidosis	1 (0.06)

Comment

This observational study examined the efficacy and safety of Viekira Pak/Viekira Pak-RBV in 1,567 Spanish patients in a real world clinical setting, where patient populations are more diverse and complex than in clinical trials.

Three patients (0.19%) experienced serious psychiatric disorders, although there was no additional information about the type of psychiatric disorder, how the psychiatric disorders were diagnosed or whether the patients took concomitant RBV or not.

3.2 Company reports

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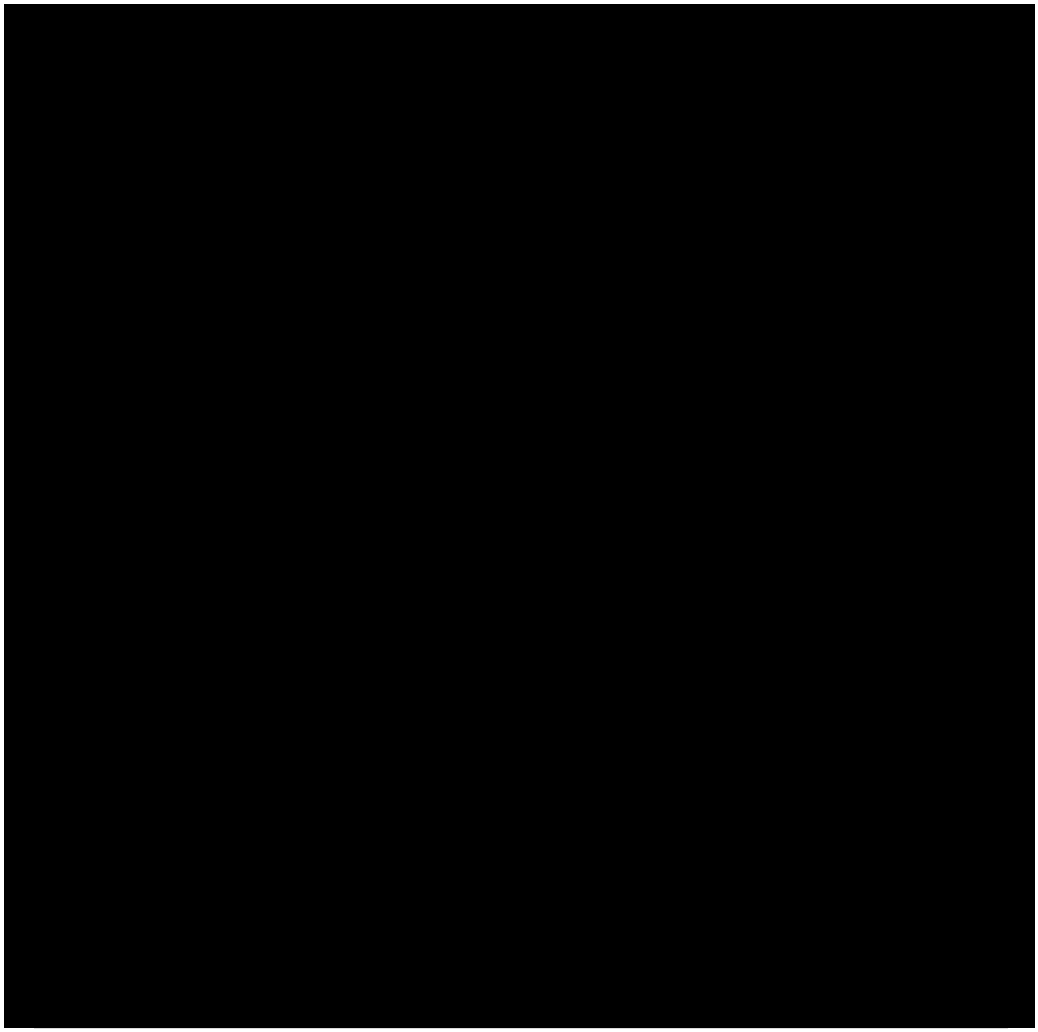

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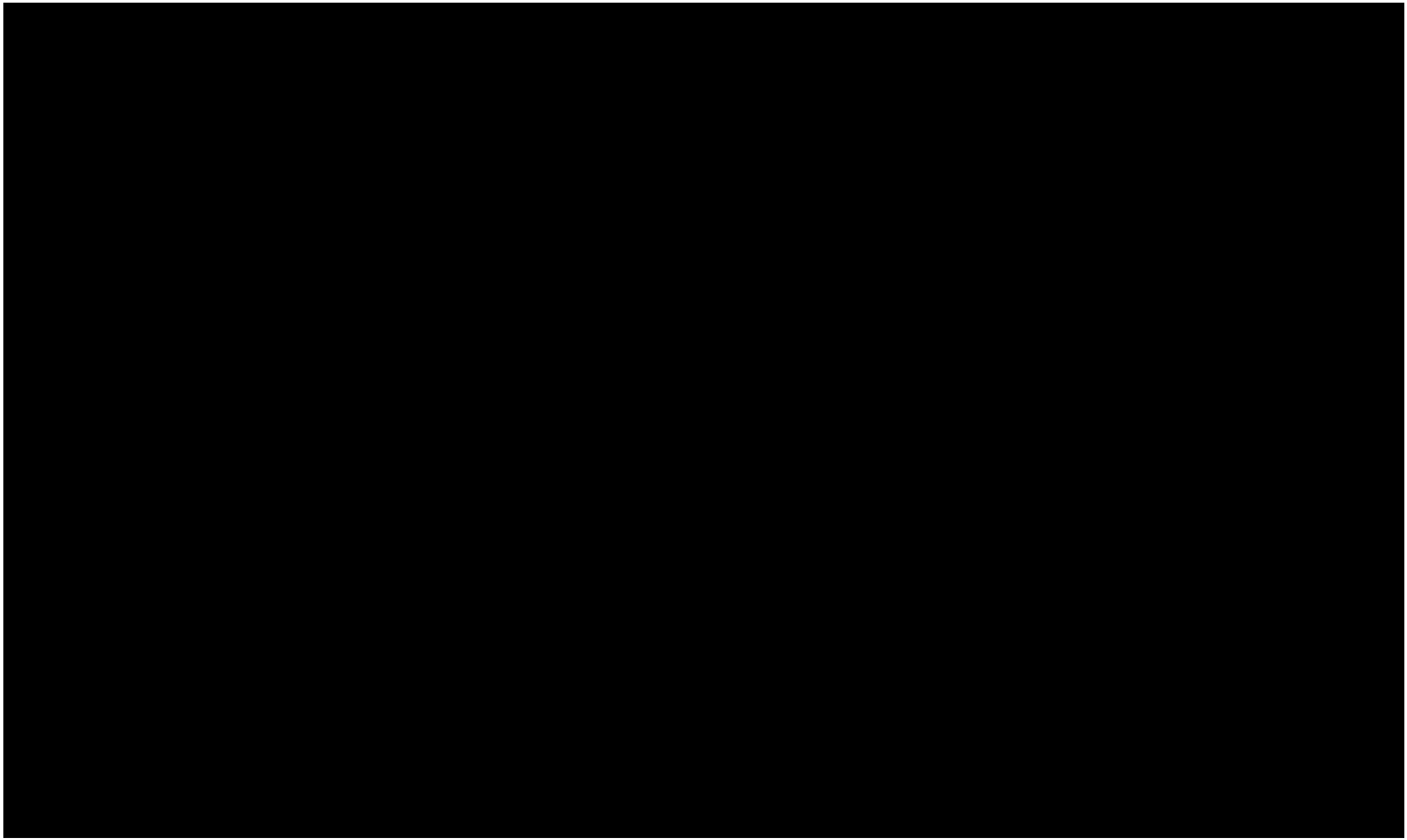

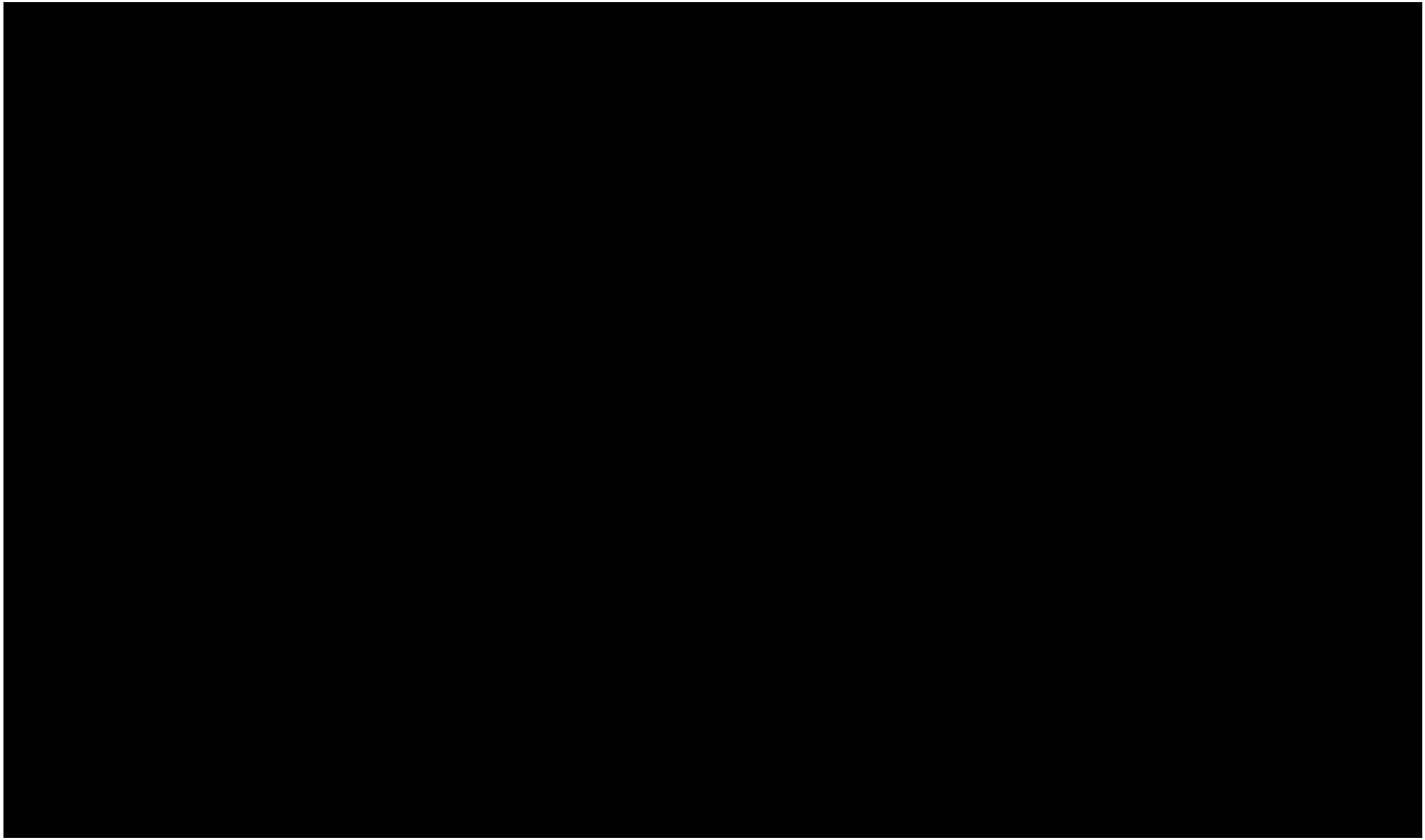

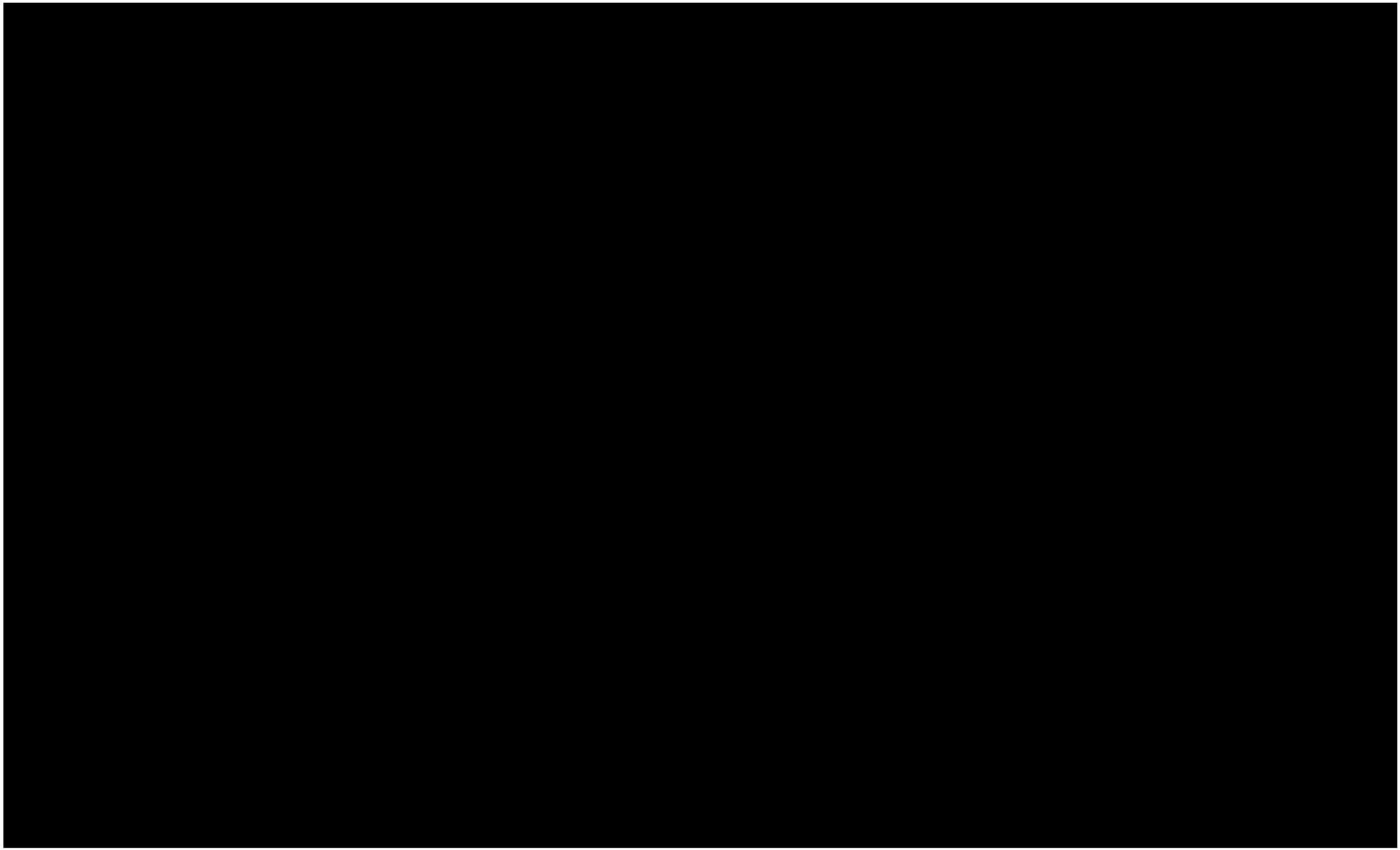

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4.0 DISCUSSION AND CONCLUSIONS

Viekira Pak and Viekira Pak-RBV (ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin) are direct-acting antivirals (DAAs), used for the treatment of chronic hepatitis C infection. The use of DAAs for the treatment of hepatitis C has largely superseded the use of treatment regimens containing pegylated interferon and ribavirin.

Viekira Pak/Viekira Pak-RBV have been funded in New Zealand since 2016, and are indicated for patients with HCV genotype 1. PHARMAC are currently reviewing a proposal to fund glecaprevir/pibrentasvir (Maviret), a pangenotypic treatment. If approved, Maviret would replace Viekira Pak/Viekira Pak-RBV.

Psychotic symptoms can be associated with a wide variety of primary psychiatric illnesses and medical illnesses or be substance- or medication-induced, all of which can confound causality assessment. Risk factors for HCV infection include injecting drug use, which can cause psychotic symptoms. The hepatitis C virus may cause neuroinflammation and lead to psychiatric changes. Interferons and peginterferons with or without ribavirin have been associated with severe psychiatric changes including hallucinations and psychosis, and ribavirin is independently associated with depressive symptoms. DAAs, including Viekira Pak and Viekira Pak-RBV, are known to interact with many other medications, the consequences of which may lead to sub-optimal disease/symptom management, drug toxicity or possible non-adherence. However, there is no published literature identifying a causal association between Viekira Pak/Viekira Pak-RBV and severe psychiatric changes.

The Viekira Pak/Viekira Pak-RBV data sheets do not list psychotic disorder or hallucinations as potential adverse events. They do refer to the currently approved ribavirin data sheet (Copegus) for information about ribavirin-related adverse events, which includes hallucinations and psychotic disorder. However, Copegus is a Roche product whereas the ribavirin tablets included with Viekira Pak-RBV are an AbbVie product.

[redacted]

5.0 ADVICE SOUGHT

The Committee is asked to advise whether there is sufficient evidence for an association between Viekira Pak/Viekira Pak-RBV and severe psychiatric changes, and if so:

- is a data sheet update required
- does this topic require further communication, other than MARC's remarks in *Prescriber Update.*

6.0 ANNEXES

1. AbbVie Company Report – Ombitasvir/Paritaprevir/Ritonavir with Dasabuvir and Ribavirin: Psychiatric Changes
2. Roche Drug Safety Abbreviated Report – Pegasys/peginterferon alfa-2a and Copegus/ribavirin Psychiatric Disorders: Psychotic Disorder and Hallucinations
3. NZ Society of Gastroenterology HCV Treatment Guidelines

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