▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – VOYDEYA® (DANICOPAN)

1 NAME OF THE MEDICINE

Danicopan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VOYDEYA 50 mg film-coated tablet contains 50 mg of danicopan.

Each VOYDEYA 100 mg film-coated tablet contains 100 mg of danicopan.

Excipient with known effect

Lactose monohydrate

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet.

VOYDEYA 50 mg film-coated tablets

White to off-white, round film-coated tablets, “DCN” above “50” debossed on one side, plain on the other side.

VOYDEYA 100 mg film-coated tablets

White to off-white, round film-coated tablets, “DCN” above “100” debossed on one side, plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VOYDEYA is indicated as an add-on to ravulizumab or eculizumab for the treatment of the signs or symptoms of extravascular haemolysis (EVH) in adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended starting dose is 150 mg three times a day administered orally, approximately 8 hours apart (± 2 hours). Depending on clinical response the dose can be increased to 200 mg three times a day (tid).

PNH is a chronic disease and add-on treatment with VOYDEYA is recommended to continue for the patient’s lifetime, unless the discontinuation of VOYDEYA is clinically indicated.

VOYDEYA must not be administered as monotherapy as the efficacy has not been established. It should only be prescribed as an add-on to ravulizumab or eculizumab.

Missed doses

If a dose is missed, advise patients to take it as soon as it is remembered, unless it is almost time for the next dose in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take 2 or more doses of VOYDEYA at the same time.

Discontinuation

Due to the possibility of alanine aminotransferase (ALT) elevations after treatment cessation, if VOYDEYA is discontinued, the dose should be tapered over a 6-day period until complete cessation as follows:

- 150 mg regimen: 100 mg three times a day for 3 days, followed by 50 mg three times a day for 3 days.
- 200 mg regimen: 100 mg three times a day for 3 days, followed by 100 mg twice a day for 3 days.

Method of administration

VOYDEYA can be taken with or without food (refer to *Section 5.2 Pharmacokinetic Properties*).

Dosage adjustment

Elderly

No dose adjustment is required in elderly patients.

Renal impairment

No dose adjustment is required in patients with renal impairment (refer to *Section 5.2 Pharmacokinetic Properties*).

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) (refer to *Section 5.2 Pharmacokinetic Properties*). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), therefore, VOYDEYA is not recommended in this patient population (refer to *Section 4.4 – Special Warnings and Precautions for Use*).

Paediatric population

The efficacy and safety of VOYDEYA has not been studied in paediatric population (< 18 years old).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in *Section 6.1 List of Excipients*.

Do not initiate VOYDEYA therapy in patients:

- with unresolved *Neisseria meningitidis* infection.
- with unknown history of vaccination or who are not up to date on their meningococcal vaccines as per local guidelines, unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (refer to *Section 4.4 Special Warnings and Precautions for Use*).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious Infections

Meningococcal Infections

Patients receiving complement inhibitor therapy may have increased susceptibility to meningococcal infections (*Neisseria meningitidis)*. Patients must be up to date on their meningococcal vaccines according to current national guidelines for vaccination use, prior to receiving the first dose of VOYDEYA.

Patients who initiate VOYDEYA treatment less than 2 weeks after receiving a meningococcal vaccine, must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients must be vaccinated against serogroups A, C, Y, and W135 to prevent the commonly pathogenic meningococcal serogroups. Vaccination against serogroup B, where available, is also recommended. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

All patients treated with VOYDEYA should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately. This information will be provided in the Consumer Medicines Information.

Other Serious Infections

VOYDEYA should be administered with caution to patients with active systemic infections. Danicopan selectively blocks the activation of the complement alternative pathway; therefore, patients may have increased susceptibility to serious infections (other than *Neisseria meningitidis*). Prior to initiating VOYDEYA as add-on to ravulizumab or eculizumab, it is recommended that patients initiate immunisation according to current immunisation guidelines.

Use in the elderly

No data available (Refer to *Section 4.2 Dosage and Method of Administration-Elderly*).

Paediatric use

No data available (Refer to *Section 4.2 Dosage and Method of Administration- Paediatric population).*

Effects on laboratory tests

Alanine aminotransferase (ALT) elevations have been observed in clinical trials (refer to *Section 4.8 Adverse Effects (Undesirable Effects*). It is recommended that liver enzyme tests be performed before treatment begins. Following initiation of treatment, routine chemistry laboratory monitoring as per PNH management is recommended. Consider treatment interruption or discontinuation if elevations are clinically significant or if patients become symptomatic. Studies have not been conducted in patients with severe hepatic impairment (refer to *Section 4.2 Dose and Method of Administration*).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of Danicopan on Other Medicinal Products

Dedicated clinical pharmacology studies confirmed that no clinically significant drug interactions were observed with danicopan as an inhibitor of other enzymes, i.e., CYP2B6, CYP2C9, CYP2C19, CYP3A4, UGT1A1 and UGT2B7.

P-gp substrates

Co-administration of a single oral dose of 180 mg fexofenadine, a P-gp substrate, with 150 mg three times daily (tid) of danicopan resulted in increased fexofenadine maximum observed

concentration (C_{max}) and area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$) by 1.42-fold and 1.62-fold, respectively.

Co-administration of a single oral dose of 2 mg tacrolimus, a P-gp substrate, with 200 mg tid doses of danicopan resulted in increased tacrolimus C_{max} and $AUC_{0\text{-}inf}$ by 1.13-fold and 1.49-fold, respectively.

The results suggest that danicopan is an inhibitor of P-gp. Caution may be needed in co--administering medicines that are known to be substrates of P-gp (such as dabigatran, digoxin, edoxaban, fexofenadine, tacrolimus).

BCRP substrates

Co-administration of a single oral dose of 20 mg rosuvastatin, a BCRP substrate, with 200 mg tid doses of danicopan resulted in increased rosuvastatin C_{max} and $AUC_{0\text{-}inf}$ by 3.29-fold and 2.25-fold, respectively. This result suggests that danicopan is an inhibitor of BCRP. Caution may be needed in co-administering medicines that are known to be substrates of BCRP (such as rosuvastatin and sulfasalazine).

Effects on Other Medicinal Products on Danicopan

No clinically significant drug interactions were observed for danicopan as a substrate when co-administered with antacid drugs (calcium carbonate, aluminium/magnesium hydroxide /simethicone) and a proton pump inhibitor (omeprazole).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of VOYDEYA on fertility are available.

Danicopan did not affect fertility in male and female rabbits at oral doses up to 250 mg/kg/day (yielding exposure ~8 times higher than in patients at the maximum recommended human dose [MRHD] of 200 mg three times daily based on plasma AUC). Women of childbearing potential should use effective contraception methods during treatment with VOYDEYA and until 3 days after discontinuation.

Use in Pregnancy – Category B3

There are no data from the use of VOYDEYA in pregnant women.

Placental transfer of danicopan was demonstrated in rabbits. No malformations or direct embryofetal lethality was observed with danicopan in rats or rabbits at oral doses up to 1000 mg/kg/day (yielding exposure 28- and 22-times higher in the respective species than in patients at the MRHD). Fetal weight was reduced in both species and a few rabbits aborted at this highest dose level, but this was secondary to maternal toxicity and not observed at 500 mg/kg/day (relative exposure, 18-25).

As a precautionary measure, it is preferable to avoid the use of VOYDEYA during pregnancy.

Use in Lactation

There are no data on the presence of danicopan in human milk, or on the effects of VOYDEYA on the breast fed child or on milk production. Danicopan was shown to be readily excreted in milk in rabbits, with concentrations of the drug in milk 3.5-5.5 times higher than in maternal plasma. A risk to the newborns/infants cannot be excluded, hence VOYDEYA should not be used during breastfeeding and breastfeeding should not be initiated until 3 days after treatment

discontinuation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

VOYDEYA is expected to have no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

The data described below reflect the exposure of 86 adult patients with PNH experiencing signs or symptoms of EVH who received VOYDEYA (n = 57) or placebo (n = 29) as add-on therapy to ravulizumab or eculizumab at the recommended dosing regimens for 12 weeks in the randomized, double-blind, placebo-controlled Phase 3 study.

The most frequent adverse event (≥ 10%) with VOYDEYA was headache.

Table 1 describes adverse events reported in ≥ 5% of patients treated with VOYDEYA and greater than placebo in the randomised control period of PNH Study ALXN2040-PNH-301.

Serious adverse events were reported in 3 (5.3%) patients with PNH receiving VOYDEYA. The serious adverse events in patients treated with VOYDEYA included pancreatitis and blood bilirubin increased. No serious adverse event was reported in more than 1 patient treated with VOYDEYA.

Table 1: Adverse Events Reported in ≥ 5% of VOYDEYA Treated Patients with PNH and Greater than Placebo

Body System **Adverse Event**	**Number of Patients**	
	VOYDEYA (add-on with ravulizumab or eculizumab) N = 57 **n (%)**	**Placebo (ravulizumab or eculizumab only)** N = 29 **n (%)**
Gastrointestinal Disorders		
Vomiting	3 (5.3)	0 (0.0)
General Disorders and Administration Site Conditions		
Pyrexia	3 (5.3)	0 (0.0)
Investigations		
Hepatic enzyme increased[a]	5 (8.8)	1 (3.4)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (7.0)	2 (6.9)
Pain in extremity	3 (5.3)	0 (0.0)
Nervous System Disorders		
Headache	6 (10.5)	3 (10.3)
Vascular Disorders		
Hypertension	3 (5.3)	1 (3.4)

[a] Hepatic enzyme increased includes Preferred Terms alanine aminotransferase increased, hepatic function abnormal, and hepatic enzyme increased

Of the 86 patients enrolled and randomised in Study ALXN2040-PNH-301, 71 patients had completed the 12-week randomised control period and entered the open label period (weeks 13 to 24) as of the interim data cut. Ten (10) patients remained ongoing in the 12-week randomised control period. Subsequently, all 71 patients received VOYDEYA as an add-on therapy to ravulizumab or eculizumab at the recommended dosing regimen for up to 24 weeks. Additional

serious adverse events were reported in 6 patients (8.5%). Additional adverse events reported in > 5% of patients treated with VOYDEYA in the open label period based on interim data from weeks 13 to 24, as compared to the 12-week randomised control period in Table 1, were diarrhoea (11.3%), asthenia (5.6%), fatigue (5.6%), and nausea (5.6%).

Description of selected adverse reactions

Hepatic enzyme increased

In the 12-week randomised control period of Study ALXN2040-PNH-301 (refer to *Section 5.1 Pharmacodynamic Properties*), laboratory abnormalities related to elevations in alanine aminotransferase (ALT) levels were observed in 14.0% of patients on VOYDEYA compared to 3.4% of patients on placebo. In VOYDEYA treated patients, ALT elevations > 3 × the upper limit of normal (ULN) and ≤ 5 × ULN occurred in 8.8% of patients and > 5 × ULN and ≤ 10 × ULN in 5.3% of patients. There were no elevations > 10 × ULN. All patients were asymptomatic, and all elevations were transient. Some elevations occurred in the context of haemolysis. Patients with PNH may have elevated hepatic enzymes during haemolysis as part of the natural history and clinical presentation of the disease; patients with high transfusion requirements may also present with hepatic enzyme abnormalities associated with transfused iron and subsequent liver iron overload.

Two instances of possible drug induced liver injury have been reported in an ongoing randomised controlled blinded monotherapy study conducted in a non-PNH population. Mild to moderate elevation in ALT were observed in these cases, and the patients were asymptomatic. Both events resolved after stopping blinded study medication.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Single doses up to 1200 mg and multiple doses up to 800 mg twice a day (bid) have been taken in healthy volunteers. ALT elevations occurred after treatment cessation without a taper in 2 subjects who received 500 mg and 800 mg bid. All abnormal ALT findings were transient, with no evidence of hepatic function abnormality and resolved spontaneously.

In case of overdose, elevations in aminotransferase and other liver parameters may occur. General supportive measures are recommended. It is not known if VOYDEYA can be removed by dialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Danicopan binds reversibly to complement Factor D (FD) and selectively inhibits the alternative complement pathway. Danicopan prevents the cleavage of complement Factor B into the Ba and Bb fragments which are required for the formation of the alternative pathway (AP) complement component C3 convertase (C3bBb), the generation of downstream effectors including C3 fragment opsonisation, and the amplification of the terminal pathway.

In PNH, intravascular haemolysis (IVH) is mediated by the terminal membrane attack complex (MAC), while extravascular haemolysis (EVH) is facilitated by C3 fragment opsonisation. Danicopan acts proximally in the alternative pathway of the complement cascade to control preferentially C3 fragment-mediated EVH, while co-administered ravulizumab or eculizumab is anticipated to maintain control over MAC-mediated IVH.

Pharmacodynamic effects

Danicopan inhibits the AP of the complement system, as demonstrated by the decrease in *ex vivo* serum AP activity and *in vivo* plasma Bb concentration. Danicopan also reduces complement C3 fragment deposition on circulating red blood cells (RBCs) in PNH patients.

In clinical trials in patients with PNH undergoing treatment with ravulizumab or eculizumab, co-administration of VOYDEYA from 150 mg three times a day to 200 mg three times a day inhibited AP activity by > 90%. Additionally, plasma Bb levels decreased by about 50% and the fraction of circulating PNH RBCs with measured C3 fragment deposition decreased by over 50%.

Cardiac electrophysiology

Single oral doses of danicopan administered at 400 mg, 800 mg, or 1200 mg did not prolong QTc interval. There were no categorical alerts of concern regarding electrocardiogram intervals or wave form abnormalities.

Clinical trials

Paroxysmal Nocturnal Haemoglobinuria (PNH)

The efficacy and safety of VOYDEYA in adult patients with PNH who have clinically significant EVH were assessed in a multiple-region, randomised, double-blind, placebo-controlled, Phase 3 study (ALXN2040-PNH-301). The study enrolled patients with PNH with clinically significant EVH who had been treated with a stable dose of ravulizumab or eculizumab for at least the previous 6 months. Clinically significant EVH was defined by anaemia (haemoglobin [Hgb] ≤ 9.5 g/dL) with absolute reticulocyte count ≥ 120 × 10^9/L with or without transfusion support.

VOYDEYA was administered in accordance with the recommended dosing described in *Section 4.2 Dose and Method of Administration* (150 mg three times a day (tid), and up to a maximum of 200 mg tid depending on the clinical response).

Patients were evaluated for history of vaccination and had to be vaccinated against meningococcal infection prior to or at the time of initiating treatment with VOYDEYA if vaccination status within 3 years could not verified.

Patients were randomised to VOYDEYA tid or placebo tid in a 2:1 ratio for 12 weeks in addition to background ravulizumab or eculizumab treatment in both groups. After week 12, all patients received VOYDEYA as an add-on to their background ravulizumab or eculizumab treatment up to week 24. At the end of the treatment periods (week 24), patients were offered to enter a Long-Term Extension (LTE) Period and continued to receive VOYDEYA with background ravulizumab or eculizumab.

The primary endpoint was the change in Hgb level from baseline to week 12. Key secondary endpoints were the proportion of patients with Hgb increase of ≥ 2 g/dL [1.2 mmol/L] at week 12 in the absence of transfusions, the proportion of patients with transfusion avoidance through week 12, the change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at week 12, and change from baseline in absolute reticulocyte count at week 12. Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and

did not meet the protocol specified guidelines for transfusion from baseline through 12-week treatment period 1.

A pre-specified interim analysis was performed when 63 participants reached the end (either completed or discontinued) of week 12 .

There were no discontinuations due to haemolysis.

Demographic and baseline characteristics were generally balanced between treatment groups. PNH medical history was similar between VOYDEYA treatment group and the placebo control group. Table 2 presents the baseline characteristics of the patients with PNH enrolled in the study.

Table 2. Baseline Characteristics in Study ALXN2040-PNH-301

Parameter	**Statistics**	**VOYDEYA (Add-on with ULTOMIRIS or SOLIRIS)** N = 42	**Placebo (Add-on with ULTOMIRIS or SOLIRIS)** N = 21
Age (years)	Mean (SD) Median Min, max	55 (15.64) 57.5 25, 80	53.1 (14.27) 53 29, 75
Sex Male Female	n (%)	 19 (45.2) 23 (54.8)	 7 (33.3) 14 (66.7)
Haemoglobin level (g/dL)	Mean (SD) Median	7.66 (0.939) 7.75	7.74 (1.035) 7.80
Reticulocyte count (10^9/L)	N Mean (SD) Median	42 236.37 (91.381) 211.95	20 240.64 (120.279) 209.85
Number of patients with pRBC/whole blood transfusions within 24 weeks prior to first dose	n (%)	38 (90.5)	17 (81)
pRBC/whole blood Transfusions within 24 weeks prior to first dose	Mean (SD) Median	2.5 (2.16) 2.0	2.6 (2.11) 3.0
LDH (U/L)	N Mean (SD) Median	42 298.73 (105.707) 261.0	20 278.25 (68.404) 257.25
FACIT-Fatigue score	Mean (SD) Median	33.46 (11.089) 36.0	33.86 (10.781) 37.0
Background treatment with: ULTOMIRIS or SOLIRIS	n (%)	27 (64.3) 15 (35.7)	10 (47.6) 11 (52.4)

Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; N = number of patients; pRBC = packed red blood cells; SD = standard deviation

VOYDEYA as an add-on to ravulizumab or eculizumab was superior to placebo as an add-on to ravulizumab or eculizumab and resulted in a highly statistically significant and clinically meaningful increase in Hgb from baseline to week 12. The least squares (LS) mean (standard error [SE]) increase in Hgb was 2.94 (0.211) g/dL in the VOYDEYA group compared with 0.50 (0.313) g/dL in the placebo group. The treatment group difference was 2.44 (0.375) g/dL ($p < 0.0001$) (refer to Table 3 and Figure 1). A statistically significant difference was observed as early as week 1 and a clinically meaningful effect on Hgb was seen as early as week 2.

VOYDEYA also achieved statistically significant improvement compared to placebo for all four (4) key secondary endpoints (refer to Table 3).

A significantly greater proportion of patients with PNH who have clinically significant EVH reached a Hgb increase of ≥ 2 g/dL in the absence of transfusion at Week 12 in the VOYDEYA group (59.5%) compared to the placebo group (0%).

A significantly greater proportion of patients with PNH who have clinically significant EVH achieved transfusion avoidance through Week 12 in the VOYDEYA group (83.3%) compared to the placebo group (38.1%), representing a clinical benefit for the patients.

Compared with placebo-treated patients, patients with PNH who have clinically significant EVH treated with VOYDEYA had significantly greater mean and clinically meaningful increases from baseline to week 12 in FACIT-Fatigue score, indicating improvement of fatigue. A change in score of ≥ 5 points is considered clinically meaningful.

Patients with PNH who have clinically significant EVH treated with VOYDEYA also had significantly greater mean decreases from baseline to week 12 in absolute reticulocyte count (decrease by 83.8 10^9/L) compared to the placebo group (increase by 3.5 10^9/L).

The LS mean (SE) change in lactate dehydrogenase (LDH) from baseline to week 12 was -23.49 (8.287) U/L in the VOYDEYA group and -2.92 (11.914) U/L in the placebo group; LDH levels remained controlled in both treatment groups, indicating continued control of intravascular haemolysis (IVH).

Pre-specified subgroup analyses were performed by transfusion history, screening Hgb level, Japanese ancestry, sex, race, region, age, and background C5 inhibitor (ravulizumab or eculizumab) for the primary endpoint. The improvements observed in the primary and secondary analyses were also reflected in these exploratory analyses and were generally consistent across the different subgroups tested.

Table 3: Analysis of Primary and Key Secondary Endpoints

	VOYDEYA (Add-on with ULTOMIRIS or SOLIRIS) (N = 42)	**Placebo (Add-on with ULTOMIRIS or SOLIRIS) (N = 21)**
Change in Haemoglobin Level (Primary Endpoint)		
Mean change from Baseline to week 12 (g/dL)	2.94	0.50
Treatment difference*	2.44 (95% CI: 1.69, 3.20)	
P-value	< 0.0001*	
Proportion of Patients with Haemoglobin Increase of ≥ 2 g/dL in the Absence of Transfusion		
At week 12 (%)	59.5	0
Treatment difference**	46.9 (95% CI: 29.2, 64.7)	
P-value	< 0.0001	
Proportion of Patients with Transfusion Avoidance		
Through 12-week Treatment Period (%)	83.3	38.1
Treatment difference**	41.7 (95% CI: 22.7, 60.8)	
P-value	0.0004	
Change in FACIT-Fatigue Score		
Mean change from baseline to week 12	7.97	1.85

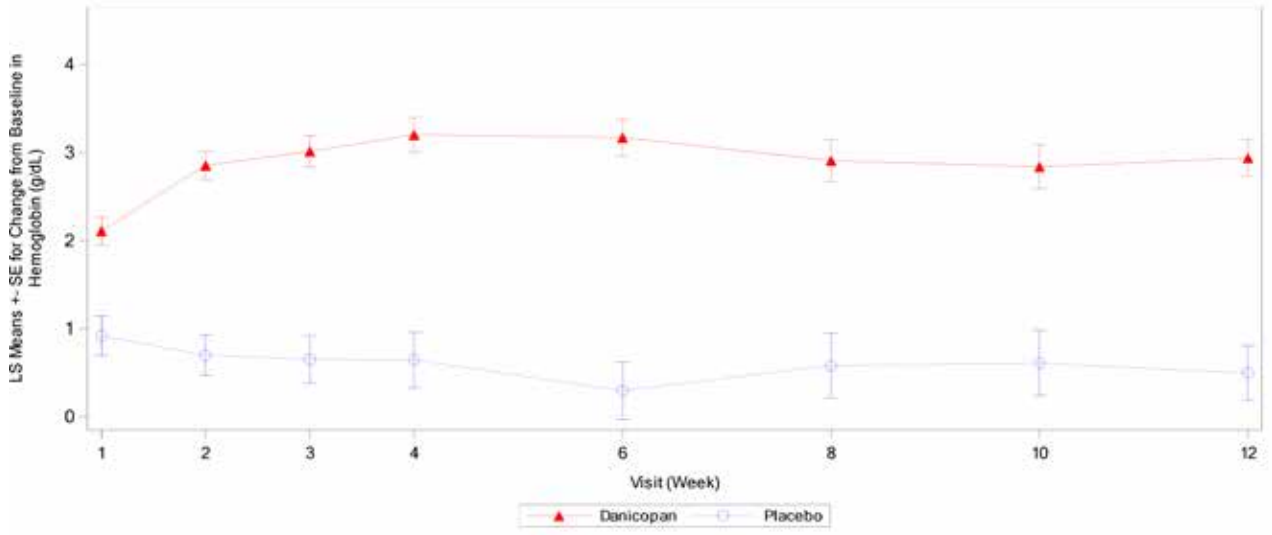
Treatment difference*	6.12 (95% CI: 2.33, 9.91)	
P-value	0.0021	
Change in Absolute Reticulocyte Count		
Mean change from baseline to week 12 (10^9/L)	-83.8	3.5
Treatment difference*	-87.2 (95% CI: -117.7, -56.7)	
P-value	< 0.0001	

(*) Based on MMRM; *Note for USPI: p =0.0007 based on rerandomisation test for the primary endpoint of change in Hgb.*

(**) Difference in rates and associated 95% CI are calculated using Miettinen and Nurminen method adjusting for stratification factors

Abbreviations: CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; MMRM = mixed-effect model for repeated measures; USPI = United States Prescribing Information

Figure 1: Mean Change in Haemoglobin Level from Baseline to Week 12



Visit	W1	W2	W3	W4	W6	W8	W10	W12
Difference[a] D - P (g/dL), LS mean (SE)	1.19 (0.273)	2.15 (0.279)	2.36 (0.320)	2.56 (0.372)	2.88 (0.384)	2.33 (0.436)	2.23 (0.447)	2.44 (0.375)

[a] p-values < 0.0001 (MMRM analysis) for treatment difference in Hgb values at Weeks 1, 2, 3, 4, 6, 8, 10, 12.

Abbreviations: D = danicopan; Hgb = hemoglobin; LS = least squares; MMRM = mixed-effect model for repeated measures; P = placebo; SE = standard error; W = week

Results at week 24 were consistent with those at week 12 and support maintenance of the effect. Among the 41 patients with PNH who have clinically significant EVH and who received VOYDEYA for 24 weeks, the LS mean (SE) increase in Hgb at week 24 was 3.17 (0.302) g/dL, 73.2% maintained transfusion avoidance through week 24 and 46.3% had a Hgb increase of ≥ 2 g/dL in the absence of transfusion at week 24. These patients also had consistent improvement in FACIT-Fatigue scores that was maintained through to 24 weeks.

LDH values were maintained through week 24. Four (4) patients had non-serious adverse events of breakthrough hemolysis (BTH) after week 12 which were assessed as unrelated to study drug and resolved without treatment modification. The LDH value at the time of the events ranged from 1.2 to 2.2 x ULN. One BTH event occurred with a COVID-19 infection. None of these events led to study discontinuation.

Data from the VOYDEYA Phase 2 study (ACH471-101) in patients with PNH who have clinically significant EVH demonstrated improvement and maintenance of the effect on Hgb for up to 3 years in a LTE.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The median time to maximum drug concentration (T_{max}) is 3.7 hours following oral administration of 150 mg danicopan in patients with PNH.

When the danicopan tablet was administered with a high-fat meal, AUC and C_{max} were approximately 25%, and 93% higher, respectively, compared to the fasted state. Median T_{max} was similar when danicopan was administered in the fed or fasted state at approximately 3.0 and 2.5 hours, respectively.

Distribution

Plasma protein binding by danicopan is high (91.5-94.3%) and primarily to human serum albumin. Danicopan is mainly distributed in plasma with a whole blood to plasma distribution ratio of 0.545.

Metabolism

Danicopan is extensively metabolised (96%) after oral dosing via oxidation, reduction, and hydrolysis pathways, with amide hydrolysis identified as the major pathway of elimination. Metabolism by CYP-mediated mechanisms is minimal.

Excretion

The mean half-life ($t_{½}$) is 7.9 hours. The mean apparent clearance of danicopan is 63 L/h.

After a single oral administration of 150 mg [^{14}C]-danicopan in humans, 69% of total radioactivity (danicopan plus metabolites) was excreted in faeces and 25% was excreted in urine. Unchanged danicopan accounted for 3.57% and 0.48% of the dose excreted in faeces and urine, respectively.

Special populations

No clinically significant differences in the pharmacokinetics of danicopan were observed based on sex, age (16.9 to 82 years), or race based on population PK assessment.

Renal impairment

Following oral administration of VOYDEYA 200 mg in subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), the extent of danicopan exposure (AUC) increased by approximately 50% as compared to subjects with normal renal function. There was no clinically meaningful change in C_{max}, T_{max}, and $t_{1/2}$. Renal excretion is not the major route for clearing danicopan from the body, even in subjects with normal renal function (refer to *Section 4.2 Dose and Method of Administration*).

Hepatic impairment

No significant difference in danicopan exposure is observed in subjects with moderate hepatic impairment (Child-Pugh Class B). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C) (see *Section 4.2 Dose and Method of Administration*).

5.3 PRECLINICAL SAFETY DATA

General toxicity

Danicopan related reversible hepatobiliary cholestasis was observed in dogs at oral doses ≥150 mg/kg/day. Exposure in animals (plasma AUC) at the no-observed-adverse-effect level

(NOAEL; 75 mg/kg/day) was ~5 times higher than in patients at the MRHD.

Phototoxicity

Danicopan binds to melanin, absorbs UV radiation, and was seen to accumulate in the eye in pigmented rats and rabbits. Ocular phototoxicity (enhanced sensitivity to focal retinopathy following UV exposure) was observed in pigmented rats treated with danicopan at oral doses ≥ 500 mg/kg/day for three days. Clinical relevance is unknown but cannot be excluded.

Genotoxicity

Danicopan was not genotoxic in the Ames bacterial reverse mutation assay, *in vitro* micronucleus assay in human peripheral blood lymphocytes or in the *in vivo* micronucleus assay in rats.

Carcinogenicity

The carcinogenic potential of danicopan was investigated in a 6-month study in transgenic (Tg.rasH2) mice and in a 2 year study in rats, both conducted by the oral route. Danicopan was not carcinogenic in either species up to the highest doses tested (1500 mg/kg/day in mice and 500 mg/kg/day in rats). These doses yield exposure to danicopan (plasma AUC) 37-77-times higher in mice and 15-23-times higher in rats than in patients at the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Lactose monohydrate

Microcrystalline cellulose

Croscarmellose sodium

Sodium lauryl sulfate

Magnesium stearate

Colloidal anhydrous silica Hypromellose acetate succinate

Film-coating

Polyvinyl alcohol

Titanium dioxide

Polyethylene glycol

Purified talc

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Bottle

Each HDPE bottle contains 90 film-coated tablets with desiccant and child resistant seal, packed inside a carton. Each carton contains 2 bottles (180 film-coated tablets).

Pack sizes:

- VOYDEYA 50 mg and 100 mg film-coated tablets: each pack contains 1 bottle of 90 × 50 mg film-coated tablets and 1 bottle of 90 × 100 mg film-coated tablets
- VOYDEYA 100 mg film-coated tablets: each pack contains 2 bottles of 90 × 100 mg film-coated tablets.

Blister packs

PVC/PCTFE/PVC blister with aluminium foil._Each pack contains 168 film-coated tablets.

Pack sizes:

- VOYDEYA 50 mg and 100 mg film-coated tablets: each pack contains 4 blister wallet cards, each containing 21 × 50 mg film-coated tablets and 21 × 100 mg film-coated tablets
- VOYDEYA 100 mg film-coated tablets: each pack contains 4 blister wallet cards, each containing 42 × 100 mg film-coated tablets.

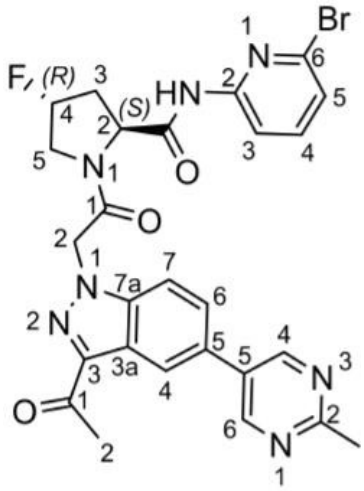
Note: Not all pack sizes are availble.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



(2S,4R)-1-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide

$C_{26}H_{23}BrFN_7O_3$

CAS number

CAS registry number: 1903768-17-1

Danicopan is a white/off-white to pale yellow powder, with dissociation constants (pKa) of 1.98 (Base) and 11.27 (Acid) and a molecular weight of 580.41. Danicopan is considered soluble at approximately pH 1.2 sparingly soluble at pHs 4 to 7, and has a partition coefficient of 2.72.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Alexion Pharmaceuticals Australasia Pty Ltd
Level 4, 66 Talavera Road
Macquarie Park, NSW, 2113

Medical enquiries: 1800 788 189

9 DATE OF FIRST APPROVAL

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