VOYDEYA®
(danicopan)

1. NAME OF THE MEDICINAL PRODUCT

VOYDEYA 50 mg film-coated tablets
VOYDEYA 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VOYDEYA 50 mg film-coated tablets

Each film-coated tablet contains 50 mg of danicopan.

VOYDEYA 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of danicopan.

Excipient with known effect

Each 50 mg tablet contains 57.5 mg of lactose in form of lactose monohydrate.
Each 100 mg tablet contains 115 mg of lactose in form of lactose monohydrate.

For the full list of excipients, see section 6.1.

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. Each tablet is approximately 8 mm.

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. Each tablet is approximately 10.3 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VOYDEYA is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated by a healthcare professional experienced in the management of patients with haematological disorders.

Posology

The recommended starting dose is 150 mg three times a day administered orally, approximately 8 hours apart (± 2 hours). Dose can be increased to 200 mg three times a day after a minimum of 4 weeks of treatment depending on clinical response.

Missed doses

If a dose is missed, patients should be advised 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 medicinal product at the next regularly scheduled time. Patients should be advised not to take 2 doses or more at the same time.

Discontinuation

Due to the possibility of alanine aminotransferase (ALT) elevations after treatment cessation (see section 4.4), if treatment is discontinued, the dose should be tapered over a 6-day period until complete cessation, as follows:

- 100 mg regimen: 100 mg twice a day for 3 days, followed by 100 mg once a day for 3 days.
- 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.

Special populations

Elderly

No dose adjustment is required in elderly patients. However, experience with VOYDEYA in patients ≥ 65 years of age is limited (see section 5.1).

Renal impairment

No dose adjustment is required in patients with mild (estimated glomerular filtration rate [eGFR] ≥ 60 to < 90 mL/min/1.73 m^2) or moderate (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) renal impairment. In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), the recommended starting dose is 100 mg three times a day administered orally, approximately 8 hours apart (± 2 hours). Dose can be increased to 150 mg three times a day after a minimum of 4 weeks of treatment depending on clinical response (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment (see section 5.2). Studies have not been conducted in patients with severe (Child-Pugh Class C) hepatic impairment. Therefore, VOYDEYA is not recommended in this patient population (see section 4.4).

Paediatric population

The safety and efficacy of VOYDEYA in children aged less than 18 years have not yet been established. No data are available.

Method of administration

Oral use.

Tablets should be taken with food (meal or snack) (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with unresolved *Neisseria meningitidis* infection at treatment initiation (see section 4.4).
- Patients who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see section 4.4).

4.4 Special warnings and precautions for use

General

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.

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 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.

Other serious infections

VOYDEYA should be administered with caution to patients with active systemic infections. VOYDEYA 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.

Severe renal impairment

Patients with severe renal impairment that dose escalate to 150 mg three times a day should be monitored for adverse events during treatment with VOYDEYA due to higher exposure expected in these patients.

Low body weight

Patients weighing < 60 kg should be monitored for adverse events during treatment with VOYDEYA due to higher exposure expected in these patients.

Hepatic enzymes increase

Alanine aminotransferase (ALT) elevations have been observed in clinical trials (see section 4.8). It is recommended that liver enzyme tests are performed before treatment begins. Following initiation of treatment, routine chemistry laboratory monitoring as per PNH management is recommended. Treatment interruption or discontinuation should be considered if elevations are clinically significant or if patients become symptomatic. VOYDEYA is not recommended in patients with severe hepatic impairment (see section 4.2).

Discontinuation

At doses higher than 200 mg three times a day, ALT elevations occurred after treatment cessation without dose tapering in healthy subjects (see section 4.9). Upon discontinuation, the dose should be tapered over 6 days (see section 4.2).

Excipients with known effect

Lactose

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of VOYDEYA on other medicinal products

P-gp substrates

Co-administration of a single oral dose of 180 mg fexofenadine, a P-gp substrate, with 150 mg three times daily doses of VOYDEYA resulted in increased fexofenadine C_{max} and $AUC_{0\text{-}inf}$ by 1.42-fold and 1.62-fold, respectively. The results suggest that VOYDEYA is a mild inhibitor of P-gp. Caution may be needed in co-administering medicinal products 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 three times daily doses of VOYDEYA resulted in increased rosuvastatin C_{max} and $AUC_{0\text{-}inf}$ by 3.29-fold and 2.25-fold, respectively. This result suggests that VOYDEYA is an inhibitor of BCRP. Caution may be needed in co-administering medicinal products that are known to be substrates of BCRP (such as rosuvastatin and sulfasalazine).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of VOYDEYA in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at therapeutically relevant dose (see section 5.3). As a precautionary measure, it is preferable to avoid the use of VOYDEYA during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of VOYDEYA/metabolites in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. VOYDEYA should not be used during breast-feeding and breast-feeding should not be initiated until 3 days after treatment discontinuation.

Fertility

No human data on the effect of VOYDEYA on fertility are available. Animal studies have shown potential effects on male fertility and reproductive performance (see section 5.3).

4.7 Effects on ability to drive and use machines

VOYDEYA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are pyrexia (25.0%), headache (19.8%), hepatic enzyme increased (11.5%), and pain in extremity (11.5%).

Tabulated list of adverse reactions

Table 1 includes adverse reactions reported in clinical trials with VOYDEYA. Adverse reactions are listed by system organ class and preferred term using MedDRA frequency convention very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Tabulated list of adverse reactions

MedDRA system order Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)
Nervous system disorders	Headache	
Vascular disorders		Hypertension
Gastrointestinal disorders		Vomiting
Hepatobiliary disorders	Hepatic enzyme increased[a]	
Musculoskeletal and connective tissue disorders	Pain in extremity	
General disorders and administration site conditions	Pyrexia	

[a] Hepatic enzyme increased includes preferred terms alanine aminotransferase increased, hepatic function abnormal, hepatic enzyme increased, and transaminases increased.

Description of selected adverse reactions

Hepatic enzyme increase

During the 12-week randomised controlled period of study ALXN2040-PNH-301 laboratory abnormalities related to elevations in ALT levels were observed in 14.0% of patients on VOYDEYA. 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. All patients were asymptomatic, and all elevations were transient. Some elevations occurred in the context of haemolysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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.

4.9 Overdose

Single doses up to 1200 mg and multiple doses up to 800 mg twice a day 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 twice a day for 14 days. 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 whether VOYDEYA can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Complement inhibitors, ATC code: L04AJ09

Mechanism of action

VOYDEYA binds reversibly to complement factor D (FD) and acts as a selective inhibitor of FD function. By inhibiting FD, VOYDEYA selectively blocks the activation of complement alternative pathway (AP), leading to prevention of the production of multiple effectors, that include C3 fragments, after AP activation. The 2 other complement pathways (classical and lectin) remain active. VOYDEYA's inhibitory effect on AP activation inhibits the deposition of C3 fragments on PNH red blood cells; such deposition is a key cause of the EVH which can become clinically significant in a small subset of patients with PNH on a C5 inhibitor. Maintenance of C5 inhibition controls the life-threatening pathophysiological consequences of terminal complement activation underlying PNH.

Pharmacodynamic effects

In a clinical trial in patients with PNH with clinically significant EVH treated with ravulizumab or eculizumab, VOYDEYA demonstrated the expected inhibition of AP activity, reduction of plasma Bb (a cleaved product of complement factor B by FD) level, as well as decreased C3 fragment deposition on circulating PNH red blood cells.

Cardiac electrophysiology

Single oral doses of VOYDEYA 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 efficacy and safety

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 86 patients with PNH who had been treated with a stable dose of ravulizumab or eculizumab for at least the previous 6 months and had anaemia (haemoglobin [Hgb] ≤ 9.5 g/dL [5.9 mmol/L]) 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 (150 mg three times a day, and up to a maximum of 200 mg three times a day 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 or placebo three times a day 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.

Demographic or baseline characteristics were generally balanced between treatment groups. PNH medical history was similar between the treatment group and the placebo control group. The mean age at baseline was 52.8 years and the majority of patients were female (62.8%). Mean haemoglobin levels at baseline were 7.75 g/dL [4.81 mmol/L] and mean reticulocyte counts were 239.40 × 10^9/L. Within 24 weeks prior to the first dose, 76 patients (88.4%) had pRBC/whole blood transfusions and the mean number of transfusion instances was 2.6. Mean LDH levels were 298.13 U/L and mean FACIT-Fatigue scores were 33.24. The study enrolled 51 patients (59.3%) on ravulizumab and 35 patients (40.7%) on eculizumab.

The primary endpoint was the change in Hgb level from baseline to week 12. 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.

The primary evidence for efficacy analysis is based on a pre-specified analysis performed when the first 63 randomised participants reached the end (either completed or discontinued) of the 12-

week treatment period 1. VOYDEYA as an add-on to ravulizumab or eculizumab was superior to placebo as an add-on to ravulizumab or eculizumab for the primary endpoint and resulted in a statistically significant increase in Hgb from baseline to week 12. The LS mean change in Hgb from baseline was 2.94 g/dL [1.82 mmol/L] in the VOYDEYA group compared with 0.50 g/dL [0.31 mmol/L] in the placebo group. The treatment group difference was 2.44 g/dL [1.51 mmol/L] (95% CI: 1.69 [1.05], 3.20 [1.99]); $p < 0.0001$). VOYDEYA also achieved statistically significant improvement compared to placebo for all 4 secondary endpoints: proportion of patients with Hgb increase of ≥ 2 g/dL [1.2 mmol/L] in the absence of transfusion (59.5% vs. 0%, treatment difference: 46.9 [95% CI: 29.2, 64.7]; $p < 0.0001$), proportion of patients with transfusion avoidance (83.3% vs. 38.1%, treatment difference: 41.7 [95% CI: 22.7, 60.8]; $p = 0.0004$), change in FACIT-Fatigue score (7.97 vs. 1.85, treatment difference: 6.12 [95% CI: 2.33, 9.91]; $p = 0.0021$) and change in absolute reticulocyte count (-83.8 vs. 3.5, treatment difference: -87.2 [95% CI: -117.7, -56.7]; $p < 0.0001$).

Supplemental results at week 12 based on all randomised patients (N = 86) are consistent with those from the primary efficacy analysis (N = 63). VOYDEYA as an add-on to ravulizumab or eculizumab was superior to placebo as an add-on to ravulizumab or eculizumab for the primary endpoint and resulted in a statistically significant increase in Hgb from baseline to week 12 (see Table 2 and Figure 1). VOYDEYA also achieved statistically significant improvement compared to placebo for all 4 secondary endpoints (see Table 2).

During the 12-week treatment period 1, 14 of 57 (24.6%) patients in the VOYDEYA add-on group were dose escalated from 150 mg to 200 mg three times a day. Four patients (2 randomised to VOYDEYA and 2 randomised to placebo) discontinued treatment during treatment period 1. There were no discontinuations due to haemolysis.

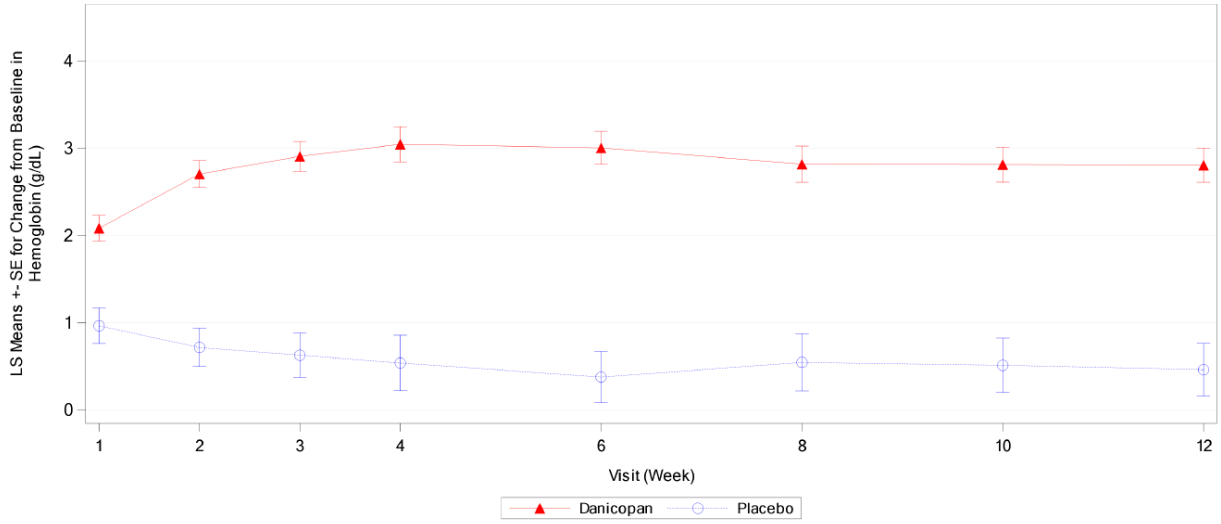
Table 2 Analysis of primary and secondary endpoints at week 12 (all randomised patients)

	VOYDEYA (add-on with ravulizumab or eculizumab) N = 57	**Placebo (add-on with ravulizumab or eculizumab) N = 29**
Change in haemoglobin level (primary endpoint)		
Mean change from baseline to week 12 (g/dL [mmol/L])	2.81 [1.74]	0.46 [0.29]
Treatment difference* (95% CI)	2.35 [1.46] (1.63 [1.01], 3.06 [1.90])	
Proportion of patients with haemoglobin increase of ≥ 2 g/dL [1.2 mmol/L] in the absence of transfusion		
At week 12 (%)	54.4	0
Treatment difference** (95% CI)	47.5 (32.6, 62.4)	
Proportion of patients with transfusion avoidance		
Through 12-week treatment period (%)	78.9	27.6

	VOYDEYA (add-on with ravulizumab or eculizumab) N = 57	Placebo (add-on with ravulizumab or eculizumab) N = 29
Treatment difference** (95% CI)	48.4 (31.8, 64.9)	
Change in FACIT-Fatigue score		
Mean change from baseline to week 12	8.10	2.38
Treatment difference* (95% CI)	5.72 (2.62, 8.83)	
Change in absolute reticulocyte count		
Mean change from baseline to week 12 (10^9/L)	-92.6	-0.9
Treatment difference* (95% CI)	-91.6 (-120.0, -63.3)	

* Based on mixed-effect model for repeated measures.
** 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

Figure 1 Mean change in haemoglobin level from baseline to week 12 (all randomised patients)



Results at week 24 were consistent with those at week 12 and support maintenance of the effect. Among the 55 patients with PNH who received VOYDEYA for 24 weeks, the LS mean change in Hgb from baseline to week 24 was 2.95 g/dL [1.83 mmol/L] (95% CI: 2.42 [1.50], 3.48 [2.16]), 69.1% maintained transfusion avoidance through week 24 and 41.8% had a Hgb increase of ≥ 2 g/dL [1.2 mmol/L] in the absence of transfusion at week 24. These patients also had consistent improvement in FACIT-Fatigue scores that was maintained through 24 weeks, the mean change from baseline was 6.19 (95% CI: 4.10, 8.29).

Efficacy results up to week 72 are consistent with those at week 12 and week 24 and support durability and maintenance of the effect over time. In patients who received VOYDEYA for 72 weeks (N = 16) the mean change in Hgb from baseline to week 72 was 2.99 g/dL [1.86 mmol/L].

5.2 Pharmacokinetic properties

Absorption

VOYDEYA is rapidly absorbed after oral dosing, with mean time to maximum observed concentration occurring at about 3 hours post dose. Over the dose range of 200 mg to 800 mg, C_{max} increased in a less than dose-proportional manner, likely due to solubility-limited absorption. When VOYDEYA 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 comparable when VOYDEYA was administered in the non-fasted or fasted state at approximately 3.0 and 2.5 hours, respectively (see section 4.2).

VOYDEYA is highly permeable and a P-gp substrate in vitro but with low efflux ratio. The oral exposure of VOYDEYA does not appear to be affected by P-gp efflux in the gastrointestinal tract. VOYDEYA is not a substrate of BCRP, OATP1B1, or OATP1B3.

Distribution

VOYDEYA is highly bound to human plasma proteins (91.5% to 94.3%) and is mainly distributed in plasma with a ratio of whole blood to plasma mean $AUC_{0-\infty}$ of 0.545. VOYDEYA plasma concentrations appeared to decline in a biphasic manner after T_{max}. The estimated oral apparent volume of distribution for a 75 kg person using the population-PK model was 168 L for Vc/F and 234 L for Vp/F (402 L total), suggesting a moderate distribution of VOYDEYA to peripheral tissue.

Biotransformation

VOYDEYA 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.

Elimination

Following oral administration, the principal route of elimination is in the faeces (approximately 69% of the administered dose, compared to approximately 25% of the administered dose in urine). In the population pharmacokinetic (PK) analysis in patients with PNH who have clinically significant EVH, the $t_{½}$ has an estimated mean value of 7.91 hours.

Special populations

No clinically significant differences in the pharmacokinetics of VOYDEYA were observed based on sex, age, 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 VOYDEYA exposure (AUC) increased by approximately 50% as compared to subjects with normal renal function. Renal excretion is not the major route for clearing VOYDEYA from the body, even in subjects with normal renal function (see section 4.2).

Hepatic impairment

No significant difference in VOYDEYA exposure is observed in subjects with moderate hepatic impairment (Child-Pugh Class B) as compared to subjects with normal hepatic function (see section 4.2). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

5.3 Preclinical safety data

In the 6-month toxicity study in rats (species not pharmacologically sensitive to VOYDEYA), hypertrophy in liver, thyroid and adrenal gland was observed at doses of 1000 mg/kg/day (~26-fold above human exposure at 200 mg three times a day based on AUC).

In the 9-month toxicity study in dogs, dose of 150 mg/kg/day was not tolerated. Target organ effects were observed in the liver consistent with hepatobiliary cholestasis and included bile duct hypertrophy/hyperplasia and pigment accumulation in Kupffer cell and hepatocyte, consistent with bile pigment. Increases in AST, ALT, ALP, GGT, and TBIL correlated with histological findings in the liver. Hypertrophy/hyperplasia of the bile duct was observed in males at doses greater than or equal to 75 mg/kg/day (~5-fold above human exposure at 200 mg three times a day based on AUC). However, the findings at the dose of 75 mg/kg/day were less in severity and magnitude and did not have correlative clinical pathology findings.

Genotoxicity/carcinogenicity

VOYDEYA 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.

VOYDEYA was not carcinogenic in the 6-month carcinogenicity study in TgRasH2 mice and in the 2-year rat carcinogenicity study. However, in the rat study a higher incidence of endometrial epithelium neoplasmas at the highest dose of 500 mg/kg/day compared to control animals was observed although the rat strain can have a high background incidence of endometrial carcinomas. The clinical relevance of this finding is unknown.

Reproductive/developmental toxicity

In the fertility and early embryonic development study in rabbits, reduced male and female reproductive performance was observed at 500 mg/kg/day, a dose associated at poor tolerability. The NOAEL for male and female reproductive toxicity was considered to be 250 mg/kg/day (7.2- and 8.8-fold above the human exposure).

In the pre- and post-natal development study in rabbits, in the F1 males, a decrease (19, 20 and 18%) in cauda epididymal sperm concentration relative to controls was observed in all dose groups (50, 125 and 250 mg/kg/day, respectively), being statistically significant only in the low and mid dose groups. This did not impact the reproductive capability of the F1 generation.

There were no effects on early embryonic development and foetal development in rabbits up to mean maternal systemic exposure ~20-fold above human exposure or during post-natal development. In the rats, there were no effects on embryo-foetal development up to maternal exposure ~30-fold above the human exposure at 200 mg three times a day.

Excretion in milk

VOYDEYA was excreted into the milk of lactating rabbits following oral administration from lactation Day 4 to 10, with milk concentrations approximately 5 and 3.5 times higher compared to maternal plasma concentrations at 50 and 250 mg/kg/day, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Cellulose, microcrystalline
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate
Silica, hydrophobic colloidal
Hypromellose acetate succinate

Film-coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months in high-density polyethylene (HDPE) bottle

After first opening the bottle: 48 days

2 years in polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE) / PVC blisters

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Bottle

HDPE bottles containing 90 film-coated tablets with desiccant and child resistant seal. Each pack contains 180 film-coated tablets.

The following pack sizes are available:

- Packs containing 1 bottle of 90 × 50 mg film-coated tablets and 1 bottle of 90 × 100 mg film-coated tablets.
- Packs containing 2 bottles of 90 × 100 mg film-coated tablets.

Blister

PVC/PCTFE/PVC blister. Each pack contains 168 film-coated tablets.

The following pack sizes are available:

- Pack containing 4 blister wallet cards (child resistant), each containing 21 × 50 mg film-coated tablets and 21 × 100 mg film-coated tablets.
- Pack containing 4 blister wallet cards (child resistant), each containing 42 × 100 mg film-coated tablets.

Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Owner

Alexion Pharmaceuticals International Operations Limited
College Business & Technology Park
Blanchardstown Road North
Dublin 15
Ireland

Date of revision of text

November 2024

11/BD/SG/VV-LAB-004363 V1.0