VENCLEXTA

1. NAME OF THE MEDICINAL PRODUCT

Venclexta (10 mg)
Venclexta (50 mg)
Venclexta (100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Venclexta (10 mg)
Each film-coated tablet contains 10 mg of venetoclax.

Venclexta (50 mg)
Each film-coated tablet contains 50 mg of venetoclax.

Venclexta (100 mg)
Each film-coated tablet contains 100 mg of venetoclax.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Venclexta (10 mg)
Pale yellow, round biconvex shaped tablet 6 mm diameter debossed with V on one side and 10 on the other.

Venclexta (50 mg)
Beige, oblong biconvex shaped tablet 14 mm long, 8 mm wide debossed with V on one side and 50 on the other.

Venclexta (100 mg)
Pale yellow, oblong biconvex shaped tablet 17.2 mm long, 9.5 mm wide debossed with V on one side and 100 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Venclexta monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.

Venclexta monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

4.2 Posology and method of administration

Treatment with Venclexta should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The starting dose is 20 mg of Venclexta once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the recommended daily dose of 400 mg as shown in Table 1.

Table 1: Dose increase schedule

Week	Venclexta daily dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

The 5-week dose-titration schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of tumour lysis syndrome (TLS).

Treatment should be continued until disease progression or no longer tolerated by the patient.

Prevention of tumour lysis syndrome
Venclexta can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of Venclexta and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter $\geq$ 5 cm or high absolute lymphocyte count [ALC $\geq$ 25 x 10^9/L]) are at greater risk of TLS when initiating Venclexta. Reduced renal function (creatinine clearance [CrCl] < 80 mL/min) further increases the risk. The risk may decrease as tumour burden decreases with Venclexta treatment (see section 4.4).

Prior to initiating Venclexta, tumour burden assessment, including radiographic evaluation (e.g., CT scan), must be performed for all patients. Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed and pre-exisiting abnormalities corrected. The prophylaxis measures listed below should be followed. More intensive measures should be employed as overall risk increases.

Hydration
Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink plenty of water daily starting 2 days before and throughout the dose-titration phase. Patients should be particularly instructed to drink 1.5 to 2.0 L of water daily, 2 days prior to and the days of dosing at initiation and each subsequent dose increase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.

Anti-hyperuricaemic agents
Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment with Venclexta in patients with high uric acid levels or at risk of TLS and may be continued through the titration phase.

Laboratory assessments
Pre-dose: For all patients, blood chemistries should be assessed prior to the initial dose to evaluate kidney function and correct pre-existing abnormalities. Blood chemistries should be reassessed prior to each subsequent dose increase during the titration phase.

Post-dose: For patients at risk of TLS, blood chemistries should be monitored at 6 to 8 hours and at 24 hours after the first dose of Venclexta. Electrolyte abnormalities should be corrected promptly. The next Venclexta dose should not be administered until the 24-hour blood chemistry results have been evaluated. The same monitoring schedule should be followed at the start of the 50 mg dose and then for patients who continue to be at risk, at subsequent dose increases.

Hospitalisation
Based on physician assessment, some patients, especially those at greater risk of TLS, may require hospitalisation on the day of the first dose of Venclexta for more intensive prophylaxis and monitoring during the first 24 hours (see section 4.8). Hospitalisation should be considered for subsequent dose increases based on reassessment of risk.

Dose modifications for tumour lysis syndrome
If a patient experiences blood chemistry changes suggestive of TLS, the following day's Venclexta dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with Venclexta can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see Table 2). When resuming treatment after interruption due to TLS, the instructions for prevention of tumour lysis syndrome should be followed (see "Prevention of tumour lysis syndrome" above).

Dose modifications for other toxicities
Treatment with Venclexta should be withheld for any grade 3 or 4 non-haematological toxicities, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia. Once the toxicity has resolved to grade 1 or baseline level (recovery), therapy with Venclexta may be restarted at the same dose. If the toxicity recurs, and for any subsequent occurrences, the dose reduction guidelines in Table 2 should be followed when resuming treatment with Venclexta following resolution. A larger dose reduction may occur at the discretion of the physician. For patients who require dose reductions to less than 100 mg for more than 2 weeks, discontinuation of Venclexta should be considered.

Table 2: Dose modification for TLS and other toxicities

Dose at interruption (mg)	**Restart dose (mg[a])**
400	300
300	200
200	100
100	50
50	20
20	10
[a]The modified dose should be continued for 1 week before increasing the dose.	

For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose titration or more than 2 weeks when at the daily dose of 400 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose titration; see Table 2).

Dose modifications for use with CYP3A inhibitors
Concomitant use of Venclexta with strong or moderate CYP3A inhibitors increases Venclexta exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities (see section 4.5).

Initiation and titration phase
Concomitant use of Venclexta with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated (see sections 4.3, 4.4, and 4.5).

Concomitant use of Venclexta with moderate CYP3A inhibitors at initiation and during the dose-titration phase should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation and titration doses of Venclexta should be reduced by at least 50%. Patients should be monitored more closely for signs of toxicities (see sections 4.4 and 4.5).

After completion of titration phase
For patients who are on a steady daily dose of Venclexta, the Venclexta dose should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors and by 75% when used concomitantly with strong CYP3A inhibitors. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The Venclexta dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see sections 4.4 and 4.5).

Missed dose
If a patient misses a dose of Venclexta within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.

If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.

Special populations

Elderly
No specific dose adjustment is required for elderly patients (aged ≥65 years) (see section 5.1).

Renal impairment
No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥ 30 mL/min and < 90 mL/min) (see section 5.2). Patients with reduced renal function (CrCl < 80 mL/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase (see "Prevention of tumour lysis syndrome" above). Safety in patients with severe renal impairment (CrCl < 30 mL/min) or on dialysis has not been established, and a recommended dose for these patients has not been determined. Venclexta should be administered to patients with severe renal impairment only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS (see section 4.4).

Hepatic impairment
No dose adjustment is recommended in patients with mild or moderate hepatic impairment, but as a trend for increased adverse events was observed in patients with moderate hepatic impairment, these patients should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase (see section 4.8).

Safety in patients with severe hepatic impairment has not been established. It is not recommended to administer Venclexta to patients with severe hepatic impairment.

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

Method of administration

Venclexta film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole with water at approximately the same time each day. The tablets should be taken with a meal in order to avoid a risk for lack of efficacy (see section 5.2). The tablets should not be chewed, crushed, or broken before swallowing.

During the dose-titration phase, Venclexta should be taken in the morning to facilitate laboratory monitoring.

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with Venclexta (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use of strong CYP3A inhibitors at initiation and during the dose-titration phase (see sections 4.2 and 4.5).

Concomitant use of preparations containing St. John's wort (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Tumour lysis syndrome

Tumour lysis syndrome, including fatal events, has occurred in patients with previously treated CLL with high tumour burden when treated with Venclexta.

Venclexta can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of Venclexta and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter $\geq$ 5 cm or high ALC $\geq$ 25 x 10^9/L) are at greater risk of TLS when initiating Venclexta. Reduced renal function (CrCl < 80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. Blood chemistries should be monitored and abnormalities managed promptly. Dosing should be interrupted if needed (see section 4.2). More intensive measures (intravenous hydration, frequent monitoring, hospitalisation) should be employed as overall risk increases. The instructions for "Prevention of tumour lysis syndrome" should be followed (see section 4.2).

Concomitant use of Venclexta with strong or moderate CYP3A inhibitors increases Venclexta exposure and may increase the risk for TLS at initiation and during the dose-titration phase (see sections 4.2 and 4.3). Also inhibitors of P-gp or BCRP may increase Venclexta exposure (see section 4.5).

Neutropenia

Grade 3 or 4 neutropenia has been reported in patients treated with Venclexta. Complete blood counts should be monitored throughout the treatment period. Dose interruptions or reductions are recommended for patients with severe neutropenia (see section 4.2). Supportive measures including antimicrobials for any signs of infection should be considered.

Immunisation

The safety and efficacy of immunisation with live attenuated vaccines during or following Venclexta therapy have not been studied. Live vaccines should not be administered during treatment and thereafter until B-cell recovery.

CYP3A inducers

Co-administration of CYP3A4 inducers may lead to decreased Venclexta exposure and consequently a risk for lack of efficacy. Concomitant use of Venclexta with strong or moderate CYP3A4 inducers should be avoided (see sections 4.3 and 4.5).

Women of childbearing potential

Women of childbearing potential must use a highly effective method of contraception while taking Venclexta (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Venclexta is predominantly metabolised by CYP3A.

Agents that may increase Venclexta plasma concentrations

CYP3A inhibitors
Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, for 7 days in 11 patients increased Venclexta C_{max} by 2.3-fold and AUC_{∞} by 6.4-fold. Co-administration of Venclexta with other strong CYP3A4 inhibitors is predicted to increase Venclexta AUC by on average 5.8- to 7.8-fold.

Concomitant use of Venclexta with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole) at initiation and during the dose-titration phase is contraindicated due to increased risk for TLS (see section 4.3).

At initiation and during the dose-titration phase, concomitant use of Venclexta with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation dose of Venclexta and the doses for the titration phase (see section 4.2) should be reduced by at least 50%. Patients should be monitored more closely for signs and symptoms of TLS.

For patients who have completed the dose-titration phase and are on a steady daily dose of Venclexta, the Venclexta dose should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors and by 75% when used concomitantly with strong CYP3A inhibitors. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The Venclexta dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see section 4.2).

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with Venclexta as they contain inhibitors of CYP3A.

P-gp and BCRP inhibitors
Venclexta is a substrate for P-gp and BCRP. Co-administration of a 600 mg single dose of rifampin, a P-gp inhibitor, in 11 healthy subjects increased Venclexta C_{max} by 106% and AUC_{∞} by 78%. Concomitant use of Venclexta with P-gp and BCRP inhibitors at initiation and during the dose-titration phase should be avoided; if a P-gp and BCRP inhibitor must be used, patients should be monitored closely for signs of toxicities (see section 4.4).

Agents that may decrease Venclexta plasma concentrations

CYP3A inducers
Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased Venclexta C_{max} by 42% and AUC_{∞} by 71%. Concomitant use of Venclexta with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered. Preparations containing St. John's wort are contraindicated during treatment with Venclexta, as efficacy may be reduced (see section 4.3).

Gastric acid reducing agents
Based on population pharmacokinetic analysis, gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect Venclexta bioavailability.

Bile acid sequestrants
Co-administration of bile acid sequestrants with Venclexta is not recommended as this may reduce the absorption of Venclexta. If a bile acid sequestrant is to be co-administered with Venclexta, the SmPC for the bile acid sequestrant should be followed to reduce the risk for an interaction, and Venclexta should be administered at least 4-6 hours after the sequestrant.

Agents that may have their plasma concentrations altered by Venclexta

Warfarin
In a drug-drug interaction study in three healthy volunteers, administration of a single dose of 400 mg Venclexta with 5 mg warfarin resulted in an 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin. Because Venclexta was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin.

Substrates of P-gp, BCRP, and OATP1B1
Venclexta is a P-gp, BCRP and OATP1B1 inhibitor *in vitro*. Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with Venclexta should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran exetilate), its administration should be separated from Venclexta administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with Venclexta, close monitoring of statin-related toxicity is recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women should avoid becoming pregnant while taking Venclexta and for at least 30 days after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking Venclexta and for 30 days after stopping treatment. It is currently unknown whether Venclexta may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

Pregnancy

Based on embryo-foetal toxicity studies in animals (see section 5.3), Venclexta may harm the foetus when administered to pregnant women.

There are no adequate and well-controlled data from the use of Venclexta in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Venclexta is not recommended during pregnancy and in women of childbearing potential not using highly effective contraception.

Breast-feeding

It is unknown whether Venclexta or its metabolites are excreted in human milk.

A risk to the breast-feeding child cannot be excluded.

Breast-feeding should be discontinued during treatment with Venclexta.

Fertility

No human data on the effect of Venclexta on fertility are available. Based on testicular toxicity in dogs at clinically relevant exposures, male fertility may be compromised by treatment with Venclexta (see section 5.3). Before starting treatment, counselling on sperm storage may be considered in some male patients.

4.7 Effects on ability to drive and use machines

Venclexta has no or negligible influence on the ability to drive and use machines. Fatigue has been reported in some patients taking Venclexta and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Summary of safety profile

The safety of Venclexta is based on pooled data of 296 patients treated with Venclexta in two phase 2 studies and one phase 1 study. In all, the studies enrolled patients with previously treated CLL, including 188 patients with 17p deletion and 92 patients who had failed a B-cell receptor pathway inhibitor. Patients were treated with Venclexta 400 mg monotherapy once daily following a dose-titration schedule.

The most commonly occurring adverse reactions (≥ 20%) of any grade in patients receiving Venclexta were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, upper respiratory tract infection, fatigue, hyperphosphataemia, vomiting, and constipation.

The most frequently reported serious adverse reactions (≥ 2%) were pneumonia, febrile neutropenia, and TLS.

Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with Venclexta are summarised in Table 3. Adverse reactions are listed below by MedDRA body system organ class and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions reported in patients with CLL treated with Venclexta

System organ class	Frequency (all grades)	Adverse Reactions (N=296)
Infections and infestations	Very common	Upper respiratory tract infection
	Common	Pneumonia Urinary tract infection
Blood and lymphatic system disorders	Very common	Neutropenia
		Anaemia
	Common	Febrile neutropenia
		Lymphopenia
Metabolism and nutrition disorders	Very common	Hyperphosphataemia
	Common	Tumour lysis syndrome Hyperkalaemia Hyperuricaemia Hypocalcaemia
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Nausea Constipation
General disorders and administration site conditions	Very common	Fatigue
Investigations	Common	Blood creatinine increased

Discontinuation and dose reductions due to ADRs
Discontinuations due to adverse reactions occurred in 9.1% of patients.

Dosage adjustments due to adverse reactions occurred in 11.8% of patients.

Description of selected adverse reactions

Tumour lysis syndrome
Tumour lysis syndrome is an important identified risk when initiating Venclexta. In the initial Phase 1 dose-finding studies, which had a shorter (2 to 3 week) titration phase and higher starting dose, the incidence of TLS was 13% (10/77; 5 laboratory TLS; 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis.

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures. In Venclexta clinical studies, patients with any measurable lymph node ≥ 10 cm or those with both an ALC ≥ 25 x 10^9/L and any measurable lymph node ≥ 5 cm were hospitalised to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the titration phase (see section 4.2).

In 122 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 3%. All events were laboratory TLS (laboratory abnormalities that met ≥ 2 of the following criteria within 24 hours of each other: potassium > 6 mmol/L, uric acid > 476 µmol/L, calcium < 1.75 mmol/L, or phosphorus > 1.5 mmol/L; or were reported as TLS events) and occurred in patients who had a lymph node(s) ≥ 5 cm or ALC ≥ 25 x 10^9/L. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥ 50 mL/min.

4.9 Overdose

There is no specific antidote for Venclexta. Patients who experience overdose should be closely monitored and appropriate supportive treatment provided. During dose-titration phase, treatment should be interrupted and patients should be monitored carefully for signs and symptoms of TLS (fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle or joint pain, abdominal pain and distension) along with other toxicities (see section 4.2). Based on Venclexta large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of Venclexta.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX52

Mechanism of action

Venclexta is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venclexta binds directly to the BH3-binding groove of BCL-2, displacing BH3 motif-containing pro-apoptotic proteins like BIM, to initiate mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death. In non-clinical studies, Venclexta has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.

Pharmacodynamic effects

Cardiac electrophysiology
The effect of multiple doses of Venclexta up to 1200 mg once daily on the QTc interval was evaluated in an open-label, single-arm study in 176 patients. Venclexta had no effect on QTc interval and there was no relationship between Venclexta exposure and change in QTc interval.

Clinical efficacy and safety

Patients with CLL harbouring 17p deletion or TP53 mutation
The safety and efficacy of Venclexta in 107 patients with previously treated CLL with 17p deletion were evaluated in a single arm, open-label, multi-center study (M13-982). Patients followed a 4- to 5-week dose-titration schedule starting at 20 mg and increasing to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive Venclexta 400 mg once daily until disease progression or unacceptable toxicity was observed. The median age was 67 years (range: 37 to 85 years); 65% were male, and 97% were white. The median time since diagnosis was 6.8 years (range: 0.1 to 32 years; N=106). The median number of prior anti-CLL treatments was 2 (range: 1 to 10 treatments); 49.5% with a prior nucleoside analogue, 38% with prior rituximab, and 94% with a prior alkylator (including 33% with prior bendamustine). At baseline, 53% of patients had one or more nodes $\geq$ 5 cm, and 51% had ALC $\geq$ 25 x 10^9/L. Of the patients, 37% (34/91) were fludarabine refractory, 81% (30/37) harboured the unmutated *IgVH* gene, and 72% (60/83) had *TP53* mutation. The median time on treatment at the time of evaluation was 12 months (range: 0 to 22 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Efficacy results are shown in Table 4. Efficacy data are presented for 107 patients with data cut-off date 30 April 2015. An additional 51 patients were enrolled in a safety expansion cohort. Investigator-assessed efficacy are presented for 158 patients with a later data cut-off date 10 June 2016. The median time on treatment for 158 patients was 17 months (range: 0 to 34 months).

Table 4: Overall response rate and duration of response (DOR) in patients with previously treated CLL with 17p deletion (Study M13-982)

Endpoint	IRC assessment (N=107)[a]	Investigator assessment (N=158)[b]
Data cut-off date	30 April 2015	10 June 2016
ORR, % (95% CI)	79 (70.5, 86.6)	77 (69.9, 83.5)
CR + CRi, %	7	18
nPR, %	3	6
PR, %	69	53
DOR, months, median (95% CI)	NR	27.5 (26.5, NR)
PFS, % (95% CI) 12-month estimate 24-month estimate	 72 (61.8, 79.8) NA	 77 (69.1, 82.6) 52 (43, 61)
PFS, months, median (95% CI)	NR	27.2 (21.9, NR)
TTR, months, median (range)	0.8 (0.1-8.1)	1.0 (0.5-4.4)

[a] One patient did not harbour the 17p deletion.
[b] Includes 51 additional patients from the safety expansion cohort.
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, IRC = independent review committee; nPR = nodular PR; NA = not available; NR = not reached; PFS = progression-free survival, PR = partial remission; TTR = time to first response.

Minimal residual disease (MRD) was evaluated using flow cytometry in 93 of 158 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with Venclexta treatment. MRD negativity was defined as a result below 0.0001 (< 1 CLL cell per 10^4 leukocytes in the sample). Twenty-seven percent (42/158) of patients were MRD negative in the peripheral blood, including 16 patients who were also MRD negative in the bone marrow.

Patients with CLL who have failed a B-cell receptor pathway inhibitor
The efficacy and safety of Venclexta in patients with CLL who had been previously treated with and failed ibrutinib or idelalisib therapy were evaluated in an open-label, multi-center, non-randomised, phase 2 study (M14-032). Patients received Venclexta via a recommended dose-titration schedule. Patients continued to receive Venclexta 400 mg once daily until disease progression or unacceptable toxicity was observed.

At the time of data cut-off, 64 patients were enrolled and treated with Venclexta. Of these, 43 patients had received prior ibrutinib therapy (Arm A) and 21 had received prior idelalisib therapy (Arm B). Of the patients, 93% (39/42) in Arm A had relapsed on or were refractory to ibrutinib and 67% (14/21) in Arm B had relapsed on or were refractory to idelalisib. The median age was 67 years (range: 48 to 85 years), 75% were male, and 92% were white. The median time since diagnosis was 8.7 years (range: 0.3 to 18.5 years; N=48). Chromosomal aberrations were 11q deletion (30%, 19/62), 17p deletion (36%, 23/61), *TP53* mutation (26%, 16/61) and unmutated *IgVH* (86%, 36/42). At baseline, 41% of patients had one or more nodes $\geq$ 5 cm and 37.5% had ALC $\geq$ 25 x 10^9/L. The median number of prior oncology treatments was 4 (range: 1 to 12) in ibrutinib-treated patients and 3 (range: 1 to 11) in idelalisib-treated patients. Overall, 69% of patients received prior nucleoside analogue, 88% rituximab, 31% other monoclonal antibodies, and 86% alkylating agent (including 42% with bendamustine). At the time of evaluation, median duration of treatment with Venclexta was 11.7 months (range: 0.1 to 17.9 months).

The primary efficacy endpoint was ORR according to IWCLL updated NCI-WG guidelines. Response assessments were performed at 8 weeks, 24 weeks, and every 12 weeks thereafter.

Table 5: Efficacy results as assessed by investigator in patients who have failed a B-cell receptor pathway inhibitor (Study M14-032)

	Arm A (ibrutinib failures) (N=43)	Arm B (idelalisib failures) (N=21)	Total (N=64)
ORR, % (95% CI)	67 (51.5, 80.9)	57 (34, 78.2)	64 (51.1, 75.7)
CR + CRi, %	7	14	9
nPR, %	5	0	3
PR, %	56	43	52
PFS, % (95% CI) 6-month estimate 12-month estimate	 88 (73.7, 94.9) 69 (50.9, 81.8)	 90 (66.2, 97.5) 84 (57.2, 94.6)	 89 (78, 94.5) 72 (56.6, 82.4)
TTR, months, median (range)	1.6 (1.6-11)	1.7 (1.6-8.1)	1.6 (1.6-11)
17p deletion/*TP53* mutation status ORR, % (95% CI)			
Yes	(n=21) 62 (38.4, 81.9)	(n=2) 100 (15.8, 100)	–
No	(n=22) 73 (49.8, 89.3)	(n=19) 53 (28.9, 75.6)	–
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, nPR = nodular PR; PR = partial remission, ORR = overall response rate; PFS = progression free survival, TTR = time to first response.			

The efficacy data were further evaluated by an IRC demonstrating a combined ORR of 67% (Arm A: 70%; Arm B: 62%). One patient (ibrutinib failure) achieved complete remission with incomplete marrow recovery. The ORR for patients with 17p deletion/*TP53* mutation was 71% (15/21) (95% CI: 47.8, 88.7) in Arm A and 50% (1/2) (95% CI: 1.3, 98.7) in Arm B. For patients without 17p deletion/*TP53* mutation, the ORR was 68% (15/22) (95% CI: 45.1, 86.1) in Arm A and 63% (12/19) (95% CI: 38.4, 83.7) in Arm B.

Median PFS and DOR were not reached with median follow up of approximately 12 months for Arm A and 9 months for Arm B.

Twenty five percent (16/64) of patients were MRD negative in the peripheral blood, including 1 patient who was also MRD negative in bone marrow.

Elderly patients

Of the 107 patients who were evaluated for efficacy from M13-982 study, 57% were 65 years or older. Of the 64 patients who were evaluated for efficacy from M14-032 study, 64% were 65 years or older.

Of the 296 patients evaluated for safety from 3 open-label trials, 57% were 65 years or older.

There were no overall differences in safety or efficacy observed between older and younger patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Venclexta in all subsets of the paediatric population in CLL (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following multiple oral administrations, maximum plasma concentration of Venclexta was reached 5-8 hours after dose. Venclexta steady state AUC increased proportionally over the dose range of 150-800 mg. Under low-fat meal conditions, Venclexta mean (± standard deviation) steady state C_{max} was 2.1 ± 1.1 µg/mL and AUC_{24} was 32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose.

Effect of food
Administration with a low-fat meal increased Venclexta exposure by approximately 3.4-fold and administration with a high-fat meal increased Venclexta exposure by 5.1- to 5.3-fold compared to fasting conditions. It is recommended that Venclexta should be administered with a meal (see section 4.2).

Distribution

Venclexta is highly bound to human plasma protein with unbound fraction in plasma < 0.01 across a concentration range of 1-30 µM (0.87-26 µg/mL). The mean blood-to-plasma ratio was 0.57. The population estimate for apparent volume of distribution (Vd_{ss}/F) of Venclexta ranged from 256-321 L in patients.

Biotransformation

In vitro studies demonstrated that Venclexta is predominantly metabolised by cytochrome P450 CYP3A4. M27 was identified as a major metabolite in plasma with an inhibitory activity against BCL-2 that is at least 58-fold lower than Venclexta *in vitro*.

In vitro interaction studies

Co administration with CYP and UGT substrates
In vitro studies indicated that Venclexta is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6 or CYP3A4 at clinically relevant concentrations. Venclexta is a weak inhibitor of CYP2C8, CYP2C9 and UGT1A1 *in vitro*, but it is not predicted to cause clinically relevant inhibition. Venclexta is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

Co administration with transporter substrates/inhibitors
Venclexta is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and a weak OATP1B1 inhibitor *in vitro* (see section 4.5). Venclexta is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K at clinically relevant concentrations.

Elimination

The population estimate for the terminal phase elimination half-life of Venclexta was approximately 26 hours. Venclexta shows minimal accumulation with accumulation ratio of 1.30-1.44. After a single oral administration of 200 mg radiolabeled [^{14}C]-Venclexta to healthy subjects, > 99.9% of the dose was recovered in faeces and < 0.1% of the dose was excreted in urine within 9 days. Unchanged Venclexta accounted for 20.8% of the administered radioactive dose excreted in faeces. The pharmacokinetics of Venclexta do not change over time.

Special populations

Renal impairment
Based on a population pharmacokinetic analysis that included 219 subjects with mild renal impairment (CrCl ≥ 60 and < 90 mL/min), 86 subjects with moderate renal impairment (CrCl ≥ 30 and < 60 mL/min) and 217 subjects with normal renal function (CrCl ≥ 90 mL/min), Venclexta exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. The pharmacokinetics of Venclexta has not been studied in subjects with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis (see section 4.2).

Hepatic impairment
Based on a population pharmacokinetic analysis that included 74 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 442 subjects with normal hepatic function, Venclexta exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin > 1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin > 1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin > 3.0 ULN. The pharmacokinetics of Venclexta has not been studied in subjects with severe hepatic impairment (see section 4.2).

Effects of age, sex, and weight

Based on population pharmacokinetic analyses, age, sex, and weight do not have an effect on Venclexta clearance.

5.3 Preclinical safety data

Toxicities observed in animal studies with Venclexta included dose -dependent reductions in lymphocytes and red blood cell mass. Both effects were reversible after cessation of dosing with Venclexta, with recovery of lymphocytes occurring 18 weeks post treatment. Both B- and T-cells were affected, but the most significant decreases occurred with B-cells.

Venclexta also caused single cell necrosis in various tissues, including the gallbladder and exocrine pancreas, with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude.

After approximately 3 months of daily dosing in dogs, Venclexta caused progressive white discoloration of the hair coat, due to loss of melanin pigment in the hair.

Carcinogenicity/gentotoxicity

Carcinogenicity studies have not been conducted with Venclexta.

Venclexta was not genotoxic in bacterial mutagenicity assay, *in vitro* chromosome aberration assay and *in vivo* mouse micronucleus assay. The M27 metabolite was negative for genotoxicity in the bacterial mutagenicity and chromosomal aberration assays.

Reproductive toxicity

No effects on fertility were observed in fertility and early embryonic development studies in male and female mice. Testicular toxicity (germ cell loss) was observed in general toxicity studies in dogs at exposures of 0.5 to 18 times the human AUC exposure at the recommended dose. Reversibility of this finding has not been demonstrated.

In embryo-foetal development studies in mice, Venclexta was associated with increased post-implantation loss and decreased foetal body weight at exposures of 1.1 times the human AUC exposure at the recommended dose. In rabbits, Venclexta produced maternal toxicity, but no foetal toxicity at exposures of 0.1 times the human AUC exposure at the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Venclexta (10 mg)

Tablet core
Copovidone, K value 28
Colloidal anhydrous silica (E551)
Polysorbate 80 (E433)
Sodium stearyl fumarate
Anhydrous calcium hydrogen phosphate (E341 (ii))

Film-coating
Iron oxide yellow (E172)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

Venclexta (50 mg)

Tablet core
Copovidone, K value 28
Colloidal anhydrous silica (E551)
Polysorbate 80 (E433)
Sodium stearyl fumarate
Anhydrous calcium hydrogen phosphate (E341 (ii))

Film-coating
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

Venclexta (100 mg)

Tablet core
Copovidone, K value 28
Colloidal anhydrous silica (E551)
Polysorbate 80 (E433)
Sodium stearyl fumarate
Anhydrous calcium hydrogen phosphate (E341 (ii))

Film-coating
Iron oxide yellow (E172)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Venclexta (10 mg) and Venclexta (50 mg): 2 years
Venclexta (100 mg): 3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Venclexta film-coated tablets are supplied in PVC/PE/PCTFE aluminium foil blisters containing either 7 or 14 film-coated tablets or in HDPE bottle containing 120 tablets.

Venclexta (10 mg)
The film-coated tablets are supplied in cartons containing 14 tablets.

Venclexta (50 mg)
The film-coated tablets are supplied in cartons containing 7 tablets.

Venclexta (100 mg)
The film-coated tablets are supplied in cartons containing either 7 or 14 tablets; or in a bottle containing 120 tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Zuellig Pharma Ltd., Bangkok, Thailand.

8. MARKETING AUTHORISATION NUMBER(S)

Venclexta (10 mg): 1C 38/61 (NC)
Venclexta (50 mg): 1C 41/61 (NC)
Venclexta (100 mg): 1C 39/61 (NC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Venclexta (10 mg): 11 MAY 2018
Venclexta (50 mg): 18 MAY 2018
Venclexta (100 mg): 11 MAY 2018

10. DATE OF REVISION OF THE TEXT

March 2019 (CCDS 04961115)