ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg film-coated tablets
Venclyxto 50 mg film-coated tablets
Venclyxto 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Venclyxto 10 mg film-coated tablets
Each film-coated tablet contains 10 mg of venetoclax.

Venclyxto 50 mg film-coated tablets
Each film-coated tablet contains 50 mg of venetoclax.

Venclyxto 100 mg film-coated tablets
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).

Venclyxto 10 mg film-coated tablet
Pale yellow, round biconvex shaped tablet 6 mm diameter debossed with V on one side and 10 on the other.

Venclyxto 50 mg film-coated tablet
Beige, oblong biconvex shaped tablet 14 mm long, 8 mm wide debossed with V on one side and 50 on the other.

Venclyxto 100 mg film-coated tablet
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

Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

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

Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

4.2 Posology and method of administration

Treatment with venetoclax should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. Patients treated with venetoclax may develop tumour lysis syndrome (TLS). Information described in this section, including risk assessment, prophylactic measures, dose-titration schedule, laboratory monitoring, and drug interactions should be followed to prevent and reduce the risk of TLS.

Posology

Chronic lymphocytic leukaemia

Dose-titration schedule

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

Table 1: Dose increase schedule in patients with CLL

Week	Venetoclax daily dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5	400 mg

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

Venetoclax in combination with obinutuzumab

Venetoclax is given for a total of 12 cycles, each cycle consisting of 28 days: 6 cycles in combination with obinutuzumab, followed by 6 cycles of venetoclax as a single agent.

Administer obinutuzumab 100 mg on Cycle 1 Day 1, followed by 900 mg which may be administered on Day 1 or Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles.

Start the 5-week venetoclax dose-titration schedule (see Table 1) on Cycle 1 Day 22 and continue through Cycle 2 Day 28.

After completing the dose-titration schedule, the recommended dose of venetoclax is 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the last day of Cycle 12.

Post-titration dose for venetoclax in combination with rituximab

The recommended dose of venetoclax in combination with rituximab is 400 mg once daily (see section 5.1 for details of the combination regimen).

Administer rituximab after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

Venetoclax is taken for 24 months from Cycle 1 Day 1 of rituximab (see section 5.1).

Post-titration dose for venetoclax monotherapy

The recommended dose of venetoclax is 400 mg once daily. Treatment is continued until disease progression or no longer tolerated by the patient.

Acute myeloid leukaemia

The recommended venetoclax dosing schedule (including dose-titration) is shown in Table 2.

Table 2: Dose increase schedule in patients with AML

Day	Venetoclax daily dose
1	100 mg
2	200 mg
3 and beyond	400 mg

Azacitidine should be administered at 75 mg/m^2 of body surface area (BSA) either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1.

Decitabine should be administered at 20 mg/m^2 of BSA intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1.

Venetoclax dosing may be interrupted as needed for management of hematologic toxicities and blood count recovery (see Table 6).

Venetoclax, in combination with a hypomethylating agent, should be continued until disease progression or unacceptable toxicity is observed.

Prevention of tumour lysis syndrome (TLS)

Patients treated with venetoclax may develop TLS. The appropriate section below should be referred to for specific details on management by disease indication.

Chronic lymphocytic leukaemia

Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase in all patients with CLL, regardless of tumour burden and other patient characteristics. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. Patient-specific factors for level of TLS risk should be assessed and prophylactic hydration and anti-hyperuricaemics should be provided to patients prior to first dose of venetoclax to reduce risk of TLS.

The risk of TLS is a continuum based on multiple factors, including comorbidities, particularly reduced renal function (creatinine clearance [CrCl] <80ml/min), and tumour burden. Splenomegaly may contribute to the overall TLS risk. The risk may decrease as tumour burden decreases with venetoclax treatment (see section 4.4).

Prior to initiating venetoclax, 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-existing abnormalities corrected.

Table 3 below describes the recommended TLS prophylaxis and monitoring during venetoclax treatment based on tumour burden determination from clinical study data (see section 4.4). In addition, all patient comorbidities should be considered for risk-appropriate prophylaxis and monitoring, either outpatient or in hospital.

Table 3: Recommended TLS prophylaxis based on tumour burden in patients with CLL

Tumour burden		**Prophylaxis**		**Blood chemistry monitoring[c,d]**
		Hydration[a]	Anti-hyperuricaemics[b]	Setting and frequency of assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent dose increases: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalisation for patients with CrCl <80ml/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 ml/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent dose increases: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.
[a]Instruct patients to drink water daily starting 2 days before and throughout the dose-titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d]At subsequent dose increases, monitor blood chemistries at 6 to 8 hours and at 24 hours for patients who continue to be at risk of TLS.

Dose modifications for tumour lysis syndrome and other toxicities

Chronic lymphocytic leukaemia

Dosing interruption and/or dose reduction for toxicities may be required. See Table 4 and Table 5 for recommended dose modifications for toxicities related to venetoclax.

Table 4: Recommended venetoclax dose modifications for toxicities[a] in CLL

Event	Occurrence	Action
Tumour lysis syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 5).
		For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 5).
Non-haematologic toxicities		
Grade 3 or 4 non-haematologic toxicities	1st occurrence	Interrupt venetoclax. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician.
Haematologic toxicities		
Grade 3 neutropenia with infection or fever; or Grade 4 haematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks. [a]Adverse reactions were graded using NCI CTCAE version 4.0. [b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or seizures and/or sudden death (see section 4.8).		

Table 5: Dose modification for TLS and other toxicities for patients with CLL

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 after completing the dose-titration phase, 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 5).

Acute myeloid leukaemia

The venetoclax daily dose-titration is 3 days with azacitidine or decitabine (see Table 2).

Prophylaxis measures listed below should be followed:
All patients should have white blood cell count $<25 \times 10^9$/l prior to initiation of venetoclax and cytoreduction prior to treatment may be required.

All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of first dose of venetoclax and during dose-titration phase.

Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during titration and 24 hours after reaching final dose.

For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase [LDH] levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.

Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status. Dose modifications of venetoclax for adverse reactions are provided in Table 6.

Table 6: Recommended dose modifications for adverse reactions in AML

Adverse Reaction	Occurrence	Dosage Modification
Haematologic Adverse Reactions		
Grade 4 neutropenia (ANC < 500/microlitre) with or without fever or infection; or grade 4 thrombocytopenia (platelet count <25 × 10^3/microlitre)	Occurrence prior to achieving remission[a]	In most instances, do not interrupt venetoclax in combination with azacitidine or decitabine due to cytopenias prior to achieving remission.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or decitabine.
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or decitabine, and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days. Refer to the azacitidine prescribing information for additional information.
Non-Hematologic Adverse Reactions		
Grade 3 or 4 non-hematologic toxicities	Any occurrence	Interrupt venetoclax if not resolved with supportive care. Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose.
[a]Consider bone marrow evaluation.		

Dose modifications for use with CYP3A inhibitors

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities (see section 4.5).

In patients with CLL, concomitant use of venetoclax with strong CYP3A inhibitors is contraindicated at initiation and during the dose-titration phase (see sections 4.3, 4.4, and 4.5).

In all patients, if a CYP3A inhibitor must be used, follow the recommendations for managing drug-drug interactions summarized in Table 7. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see sections 4.3, 4.4 and 4.5).

Table 7: Management of potential venetoclax interactions with CYP3A inhibitors

Inhibitor	Phase	CLL	AML
Strong CYP3A inhibitor	Initiation and dose-titration phase	Contraindicated	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg or less
	Steady daily dose (After dose-titration phase)	Reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons)	
Moderate CYP3A inhibitor[a]	All	Reduce the venetoclax dose by at least 50%	
[a]In patients with CLL, avoid concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative medicinal products or reduce the venetoclax dose as described in this table.			

Missed dose

If a patient misses a dose of venetoclax 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

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 (TLS)" above). Venetoclax should be administered to patients with severe renal impairment (CrCl ≥15 ml/min and <30 ml/min) 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).

No dose adjustment is needed for patients with mild, moderate or severe renal impairment (CrCl ≥15 ml/min and <90 ml/min) (see section 5.2).

Hepatic impairment

No dose adjustment is recommended in patients with mild or moderate, hepatic impairment. Patients with moderate hepatic impairment should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase (see section 4.8).

A dose reduction of at least 50% throughout treatment is recommended for patients with severe hepatic impairment (see section 5.2). These patients should be monitored more closely for signs of toxicity (see section 4.8).

Paediatric population

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

Method of administration

Venclyxto 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, venetoclax should be taken in the morning to facilitate laboratory monitoring.

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

4.3 Contraindications

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

In patients with CLL, concomitant use of strong CYP3A inhibitors at initiation and during the dose-titration phase (see sections 4.2 and 4.5).

In all patients, 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 and renal failure requiring dialysis, has occurred in patients treated with venetoclax (see section 4.8).

Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS at initiation and during the 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 venetoclax and at each dose increase. During post-marketing surveillance, TLS, including fatal events, has been reported after a single 20 mg dose of venetoclax. Information described in section 4.2, including risk assessment, prophylactic measures, dose-titration and modification schedule, laboratory monitoring, and drug interactions should be followed to prevent and reduce the risk of TLS.

The risk of TLS is a continuum based on multiple factors, including comorbidities (particularly reduced renal function), tumour burden, and splenomegaly in CLL.

All 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. More intensive measures (intravenous hydration, frequent monitoring, hospitalisation) should be employed as overall risk increases. Dosing should be interrupted if needed; when restarting venetoclax, dose modification guidance should be followed (see Table 4 and Table 5). The instructions for "Prevention of tumour lysis syndrome (TLS)" should be followed (see section 4.2).

Concomitant use of this medicinal product with strong or moderate CYP3A inhibitors increases venetoclax 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 venetoclax exposure (see section 4.5).

Neutropenia and infections

In patients with CLL, grade 3 or 4 neutropenia has been reported in patients treated with venetoclax in combination studies with rituximab or obinutuzumab and in monotherapy studies (see section 4.8).

In patients with AML, grade 3 or 4 neutropenia are common before starting treatment. The neutrophil counts can worsen with venetoclax in combination with a hypomethylating agent. Neutropenia can recur with subsequent cycles of therapy.

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).

Serious infections, including sepsis with fatal outcome, have been reported (see section 4.8). Monitoring of any signs and symptoms of infection is required. Suspected infections are to receive prompt treatment, including antimicrobials, dose interruption or reduction, and use of growth factors (e.g., G-CSF) as appropriate (see section 4.2).

Immunisation

The safety and efficacy of immunisation with live attenuated vaccines during or following venetoclax 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 venetoclax exposure and consequently a risk for lack of efficacy. Concomitant use of venetoclax 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 venetoclax (see section 4.6).

Excipients with known effect

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

Venetoclax is predominantly metabolised by CYP3A.

Agents that may alter venetoclax 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 venetoclax C_{max} to 2.3-fold and AUC to 6.4-fold. Co-administration of 50 mg once daily ritonavir, a strong CYP3A and P-gp inhibitor, for 14 days in 6 healthy subjects increased venetoclax C_{max} to 2.4-fold and AUC by 7.9-fold. Compared with venetoclax 400 mg administered alone, co-administration of 300 mg posaconazole, a strong CYP3A and P-gp inhibitor, with venetoclax 50 mg and 100 mg for 7 days in 12 patients increased venetoclax C_{max} to 1.6-fold and

1.9-fold, and AUC to 1.9-fold and 2.4-fold, respectively. Co-administration of venetoclax with other strong CYP3A4 inhibitors is predicted to increase venetoclax AUC by on average 5.8- to 7.8-fold.

For patients requiring concomitant use of venetoclax with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil), venetoclax dosing should be administered according to Table 7. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax 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 venetoclax as they contain inhibitors of CYP3A.

P-gp and BCRP inhibitors

Venetoclax is a substrate for P-gp and BCRP. Co-administration of a 600 mg single dose of rifampicin, a P-gp inhibitor, in 11 healthy subjects increased venetoclax C_{max} by 106% and AUC by 78%. Concomitant use of venetoclax 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).

CYP3A inducers

Co-administration of 600 mg once daily rifampicin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased venetoclax C_{max} by 42% and AUC by 71%. Concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampicin) 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 venetoclax, as efficacy may be reduced (see section 4.3).

Azithromycin

In a drug-drug interaction study in 12 healthy subjects, co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin once daily for 4 days decreased venetoclax C_{max} by 25% and AUC by 35%. No dose adjustment is needed during short-term use of azithromycin when administered concomitantly with venetoclax.

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 venetoclax bioavailability.

Bile acid sequestrants

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

Agents that may have their plasma concentrations altered by venetoclax

Warfarin

In a drug-drug interaction study in three healthy volunteers, administration of a single dose of 400 mg venetoclax with 5 mg warfarin resulted in an 18% to 28% increase in C_{max} and AUC of R-warfarin and S-warfarin. Because venetoclax 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

Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro*. In a drug-drug interaction study, administration of a single 100 mg dose of venetoclax with 0.5 mg digoxin, a P-gp substrate, resulted in a 35% increase in digoxin C_{max} and a 9% increase in digoxin AUC. Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with venetoclax 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 etexilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with venetoclax, 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 Venclyxto and for at least 30 days after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking venetoclax and for 30 days after stopping treatment. It is currently unknown whether venetoclax 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), venetoclax may harm the foetus when administered to pregnant women.

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

Breast-feeding

It is unknown whether venetoclax 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 Venclyxto.

Fertility

No human data on the effect of venetoclax on fertility are available. Based on testicular toxicity in dogs at clinically relevant exposures, male fertility may be compromised by treatment with venetoclax (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

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

4.8 Undesirable effects

Summary of safety profile

Chronic lymphocytic leukaemia

The overall safety profile of Venclyxto is based on data from 758 patients with CLL treated in clinical studies with venetoclax in combination with obinutuzumab or rituximab or as monotherapy. The safety analysis included patients from two phase 3 studies (CLL14 and MURANO), two phase 2 studies (M13-982 and M14-032), and one phase 1 study (M12-175). CLL14 was a randomised, controlled study in which 212 patients with previously untreated CLL and comorbidities received venetoclax in combination with obinutuzumab. MURANO was a randomised, controlled study in which 194 patients with previously treated CLL received venetoclax in combination with rituximab. In the phase 2 and phase 1 studies, 352 patients with previously treated CLL, which included 212 patients with 17p deletion and 146 patients who had failed a B-cell receptor pathway inhibitor were treated with venetoclax monotherapy (see section 5.1).

The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in the combination studies with obinutuzumab or rituximab were neutropenia, diarrhoea, and upper respiratory tract infection. In the monotherapy studies, the most common adverse reactions were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, fatigue, and upper respiratory tract infection.

The most frequently reported serious adverse reactions (≥2%) in patients receiving venetoclax in combination with obinutuzumab or rituximab were pneumonia, sepsis, febrile neutropenia, and TLS. In the monotherapy studies, the most frequently reported serious adverse reactions (≥2%) were pneumonia and febrile neutropenia.

Acute myeloid leukaemia

The overall safety profile of Venclyxto is based on data from 314 patients with newly diagnosed acute myeloid leukaemia (AML) treated in clinical studies with venetoclax in combination with a hypomethylating agent (azacitidine or decitabine) (VIALE-A phase 3 randomised, and M14-358 phase 1 non-randomised).

In the VIALE-A study, the most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in combination with azacitidine were thrombocytopenia, neutropenia, febrile neutropenia, nausea, diarrhoea, vomiting, anaemia, fatigue, pneumonia, hypokalaemia, and decreased appetite.

The most frequently reported serious adverse reactions (≥5%) in patients receiving venetoclax in combination with azacitidine were febrile neutropenia, pneumonia, sepsis and haemorrhage.
In the M14-358 study, the most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in combination with decitabine were thrombocytopenia, febrile neutropenia, nausea, haemorrhage, pneumonia, diarrhoea, fatigue, dizziness/syncope, vomiting, neutropenia, hypotension, hypokalaemia, decreased appetite, headache, abdominal pain, and anaemia. The most frequently reported serious adverse reactions (≥5%) were febrile neutropenia, pneumonia, bacteraemia and sepsis.

The 30-day mortality rate in the VIALE-A study was 7.4% (21/283) with venetoclax in combination with azacitidine and 6.3% (9/144) in the placebo with azacitidine arm.

The 30-day mortality rate in the M14-358 study with venetoclax in combination with decitabine was 6.5% (2/31).

Tabulated list of adverse reactions

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.

Chronic lymphocytic leukaemia

The frequencies of adverse reactions reported with Venclyxto, in combination with obinutuzumab, rituximab, or as monotherapy in patients with CLL are summarised in Table 8.

Table 8: Adverse drug reactions reported in patients with CLL treated with venetoclax

System organ class	Frequency	All grades[a]	Grade ≥3[a]
Infections and infestations	Very common	Pneumonia Upper respiratory tract infection	
	Common	Sepsis Urinary tract infection	Sepsis Pneumonia Urinary tract infection Upper respiratory tract infection
Blood and lymphatic system disorders	Very common	Neutropenia Anaemia Lymphopenia	Neutropenia Anaemia
	Common	Febrile neutropenia	Febrile neutropenia Lymphopenia
Metabolism and nutrition disorders	Very common	Hyperkalaemia Hyperphosphataemia Hypocalcaemia	
	Common	Tumour lysis syndrome Hyperuricaemia	Tumour lysis syndrome Hyperkalaemia Hyperphosphataemia Hypocalcaemia Hyperuricaemia
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Nausea Constipation	
	Common		Diarrhoea Vomiting Nausea
	Uncommon		Constipation
General disorders and administration site conditions	Very common	Fatigue	
	Common		Fatigue
Investigations	Common	Blood creatinine increased	
	Uncommon		Blood creatinine increased

[a]Only the highest frequency observed in the studies is reported (based on studies CLL14, MURANO, M13-982, M14-032, and M12-175).

Acute myeloid leukaemia

The frequencies of adverse reactions reported with Venclyxto in combination with a hypomethylating agent in patients with AML are summarised in Table 9.

Table 9: Adverse drug reactions reported in patients with AML treated with venetoclax

System organ class	Frequency	All grades[a]	Grade ≥3[a]
Infections and infestations	Very common	Pneumonia[b] Sepsis[b] Urinary tract infection	Pneumonia[b] Sepsis[b]
	Common		Urinary tract infection
Blood and lymphatic system disorders	Very common	Neutropenia[b] Febrile neutropenia Anaemia[b] Thrombocytopenia[b]	Neutropenia[b] Febrile neutropenia Anaemia[b] Thrombocytopenia[b]
Metabolism and nutrition disorders	Very common	Hypokalaemia Decreased appetite	Hypokalaemia
	Common	Tumour lysis syndrome	Decreased appetite
	Uncommon		Tumour lysis syndrome
Nervous System Disorders	Very common	Dizziness/syncope[b] Headache	
	Common		Dizziness/syncope[b]
	Uncommon		Headache
Vascular Disorders	Very common	Hypotension Haemorrhage[b]	Haemorrhage[b]
	Common		Hypotension
Respiratory, thoracic, and mediastinal disorder	Very common	Dyspnoea	
	Common		Dyspnoea
Gastrointestinal disorders	Very common	Nausea Diarrhoea Vomiting Stomatitis Abdominal pain	
	Common		Nausea Diarrhoea Vomiting
	Uncommon		Stomatitis
Hepatobiliary Disorders	Common	Cholecystitis/cholelithiasis[b]	Cholecystitis/cholelithiasis[b]
Musculoskeletal disorders and	Very common	Arthralgia	

connective tissue disorders	Uncommon		Arthralgia
General disorders and administration site conditions	Very common	Fatigue Asthenia	
	Common		Fatigue Asthenia
Investigations	Very common	Weight decreased Blood bilirubin increased	
	Common		Weight decreased Blood bilirubin increased
[a]Only the highest frequency observed in the studies is reported (based on studies VIALE-A and M14-358). [b]Includes multiple adverse reaction terms.			

Discontinuation and dose reductions due to adverse reactions

Chronic lymphocytic leukaemia

Discontinuations due to adverse reactions occurred in 16% of patients treated with venetoclax in combination with obinutuzumab or rituximab in the CLL14 and MURANO studies, respectively. In the monotherapy studies with venetoclax, 11% of patients discontinued due to adverse reactions.

Dosage reductions due to adverse reactions occurred in 21% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study, in 15% of patients treated with the combination of venetoclax and rituximab in the MURANO study and in 14% of patients treated with venetoclax in the monotherapy studies.

Dose interruptions due to adverse reactions occurred in 74% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study and in 71% of patients treated with the combination of venetoclax and rituximab in the MURANO study; the most common adverse reaction that led to dose interruption of venetoclax was neutropenia (41% and 43% in the CLL14 and MURANO studies, respectively). In the monotherapy studies with venetoclax, dose interruptions due to adverse reactions occurred in 40% of patients; the most common adverse reaction leading to dose interruption was neutropenia (5%).

Acute myeloid leukaemia

In the VIALE-A study, discontinuations of venetoclax due to adverse reactions occurred in 24% of patients treated with the combination of venetoclax and azacitidine. Venetoclax dosage reductions due to adverse reactions occurred in 2% of patients. Venetoclax dose interruptions due to adverse reactions occurred in 72% of patients. Among patients who achieved bone marrow clearance of leukaemia, 53% underwent dose interruptions for ANC <500/microlitre. The most common adverse reaction that led to dose interruption (>10%) of venetoclax were febrile neutropenia, neutropenia, pneumonia, and thrombocytopenia.

In the M14-358 study, discontinuations due to adverse reactions occurred in 26% of patients treated with the combination of venetoclax and decitabine. Dosage reductions due to adverse reactions occurred in 6% of patients. Dose interruptions due to adverse reactions occurred in 65% of patients; the most common adverse reactions that led to dose interruption (≥5%) of venetoclax were febrile neutropenia, neutropenia/neutrophil count decreased, pneumonia, platelet count decreased, and white blood cell count decreased.

Description of selected adverse reactions

Tumour lysis syndrome

Tumour lysis syndrome is an important identified risk when initiating venetoclax.

Chronic lymphocytic leukaemia

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 venetoclax 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 168 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg in studies M13-982 and M14-032, the rate of TLS was 2%. 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.

In the open-label, randomised phase 3 study (MURANO), the incidence of TLS was 3% (6/194) in patients treated with venetoclax + rituximab. After 77/389 patients were enrolled in the study, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in "Posology" (see section 4.2). All events of TLS occurred during the venetoclax dose-titration phase and resolved within two days. All six patients completed the dose-titration and reached the recommended daily dose of 400 mg of venetoclax. No clinical TLS was observed in patients who followed the current 5-week dose-titration schedule and TLS prophylaxis and monitoring measures (see section 4.2). The rates of grade ≥3 laboratory abnormalities relevant to TLS were hyperkalaemia 1%, hyperphosphataemia 1%, and hyperuricaemia 1%.

In the open-label, randomised phase 3 study (CLL14), the incidence of TLS was 1.4% (3/212) in patients treated with venetoclax + obinutuzumab. All three events of TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in two cases in response to the TLS events.

During post-marketing surveillance, TLS, including fatal events, has been reported after a single 20 mg dose of venetoclax (see sections 4.2 and 4.4).

Acute myeloid leukaemia

In the randomised, phase 3 study (VIALE-A) with venetoclax in combination with azacitidine the incidence of TLS was 1.1% (3/283, 1 clinical TLS). The study required reduction of white blood cell count to <25 x 10^9/l prior to venetoclax initiation and a dose-titration schedule in addition to standard prophylaxis and monitoring measures (see section 4.2). All cases of TLS occurred during dose-titration.

In M14-358 study, no events of laboratory or clinical TLS were reported with venetoclax in combination with decitabine.

Neutropenia and infections

Neutropenia is an identified risk with Venclyxto treatment.

Chronic lymphocytic leukaemia

In the CLL14 study, neutropenia (all grades) was reported in 58% of patients in the venetoclax + obinutuzumab arm; 41% of patients treated with venetoclax + obinutuzumab experienced dose interruption and 2% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 25% of patients and grade 4 neutropenia in 28% of patients. The median duration of grade 3 or 4 neutropenia was 22 days (range: 2 to 363 days). Febrile neutropenia was reported in 6% of patients, grade ≥3 infections in 19%, and serious infections in 19% of patients. Deaths due to infection occurred in 1.9% of patients while on treatment and 1.9% of patients following treatment discontinuation.

In the MURANO study, neutropenia (all grades) was reported in 61% of patients in the venetoclax + rituximab arm. Forty-three percent of patients treated with venetoclax + rituximab experienced dose interruption and 3% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 32% of patients and grade 4 neutropenia in 26% of patients. The median duration of grade 3 or 4 neutropenia was 8 days (range: 1 to 712 days). With venetoclax + rituximab treatment, febrile neutropenia was reported in 4% of patients, grade ≥3 infections in 18%, and serious infections in 21% of patients.

Acute myeloid leukaemia

In the VIALE-A study, grade ≥3 neutropenia was reported in 45% of patients. The following were also reported in the venetoclax + azacitidine arm versus the placebo + azacitidine arm, respectively: febrile neutropenia 42% versus 19%, grade ≥3 infections 64% versus 51%, and serious infections 57% versus 44%.

In the M14-358 study, neutropenia was reported in 35% (all grades) and 35% (grade 3 or 4) of patients in the venetoclax + decitabine arm.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote for venetoclax. 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 venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XX52

Mechanism of action

Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL and AML cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venetoclax 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, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.

Pharmacodynamic effects

Cardiac electrophysiology

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

Clinical efficacy and safety

Chronic lymphocytic leukaemia

Venetoclax in combination with obinutuzumab for the treatment of patients with previously untreated CLL – study BO25323 (CLL14)

A randomised (1:1), multicentre, open-label phase 3 study evaluated the efficacy and safety of venetoclax + obinutuzumab versus obinutuzumab + chlorambucil in patients with previously untreated CLL and comorbidities (total Cumulative Illness Rating Scale [CIRS] score >6 or creatinine clearance [CrCl] <70 ml/min). Patients in the study were assessed for risk of TLS and received prophylaxis accordingly prior to obinutuzumab administration. All patients received obinutuzumab at 100 mg on Cycle 1 Day 1, followed by 900 mg which could have been administered on Day 1 or Day 2, then 1000 mg doses on Days 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle, for a total of 6 cycles. On Day 22 of Cycle 1, patients in the venetoclax + obinutuzumab arm began the 5-week venetoclax dose-titration schedule, continuing through Cycle 2 Day 28. Upon completion of the dose-titration schedule, patients continued venetoclax 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. Each cycle was 28 days. Patients randomised to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1-12. Patients continued to be followed for disease progression and overall survival (OS) after completing therapy.

Baseline demographic and disease characteristics were similar between the study arms. The median age was 72 years (range: 41 to 89 years), 89% were white, and 67% were male; 36% and 43% were Binet stage B and C, respectively. The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CrCl <70 ml/min. A 17p deletion was detected in 8% of patients, *TP53* mutations in 10%, 11q deletion in 19%, and unmutated *IgVH* in 57%. The median follow-up at the time of the primary analysis was 28 months (range: 0 to 36 months).

At baseline, the median lymphocyte count was 55 x 10^9 cells/l in both study arms. On Cycle 1 Day 15, the median count had decreased to 1.03 x 10^9 cells/l (range: 0.2 to 43.4 x 10^9 cells/l) in the obinutuzumab + chlorambucil arm and 1.27 x 10^9 cells/l (range: 0.2 to 83.7 x 10^9 cells/l) in the venetoclax + obinutuzumab arm.

Progression-free survival (PFS) was assessed by investigators using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

At the time of the primary analysis (data cut-off date 17 August 2018), 14% (30/216) of patients in the venetoclax + obinutuzumab arm had a PFS event of disease progression or death compared with 36%

(77/216) in the obinutuzumab + chlorambucil arm, as assessed by investigators (hazard ratio [HR]: 0.35 [95% confidence interval [CI]: 0.23, 0.53]; p<0.0001, stratified log-rank test). Median PFS was not reached in either study arm.

Progression-free-survival was also assessed by an Independent Review Committee (IRC) and was consistent with the investigator-assessed PFS.

Investigator-assessed overall response rate (ORR) was 85% (95% CI: 79.2, 89.2) and 71% (95% CI: 64.8, 77.2) in the venetoclax + obinutuzumab and obinutuzumab + chlorambucil arms, respectively (p=0.0007, Cochran-Mantel-Haenszel test). Investigator-assessed complete remission + complete remission with incomplete marrow recovery (CR + CRi) rate was 50% and 23% in the venetoclax + obinutuzumab and obinutuzumab + chlorambucil arms, respectively (p<0.0001, Cochran-Mantel-Haenszel test).

Minimal residual disease (MRD) at the end of treatment was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) assay. MRD negativity was defined as less than one CLL cell per 10^4 leukocytes. MRD negativity rates in peripheral blood were 76% (95% CI: 69.2, 81.1) in the venetoclax + obinutuzumab arm compared to 35% (95% CI: 28.8, 42.0) in the obinutuzumab + chlorambucil arm (p<0.0001). Per protocol, MRD in bone marrow was to be assessed only in responding patients (CR/CRi and partial remission [PR]). MRD negativity rates in the bone marrow were 57% (95% CI: 50.1, 63.6) in the venetoclax + obinutuzumab arm and 17% (95% CI: 12.4, 22.8) in the obinutuzumab + chlorambucil arm (p<0.0001).

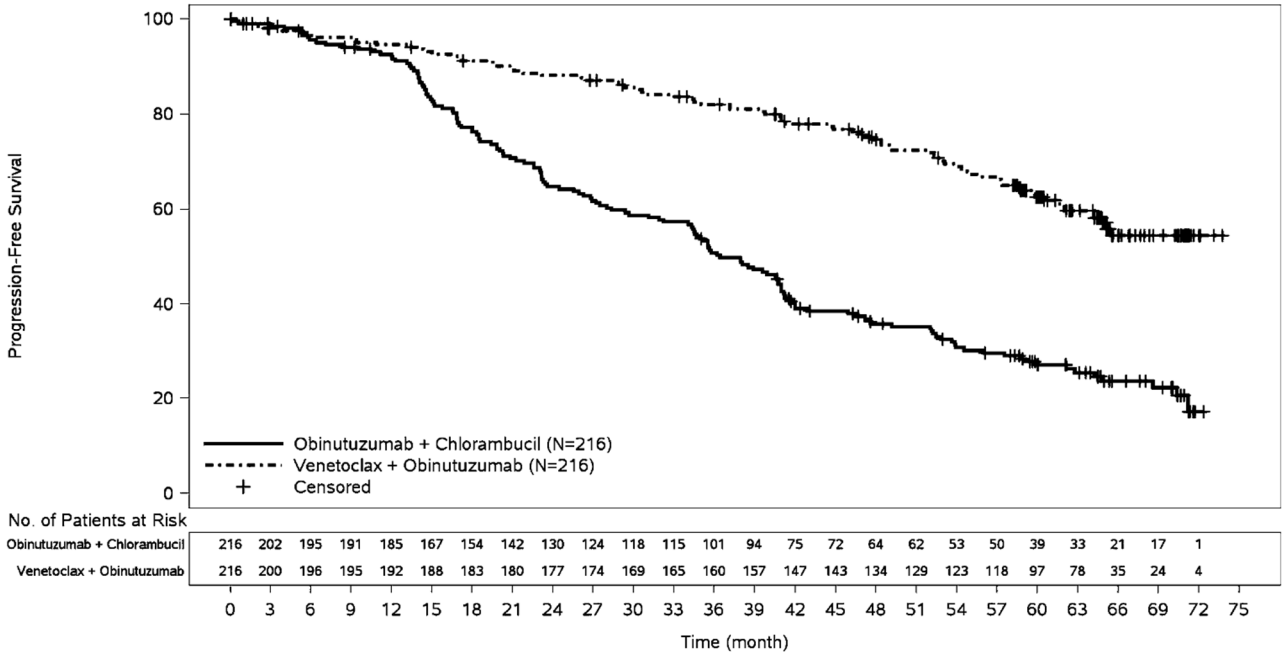
65-month follow-up

Efficacy was assessed after a median follow-up of 65 months (data cut-off date 8 November 2021). Efficacy results for the CLL14 65-month follow-up are presented in Table 10. The Kaplan-Meier curve of investigator-assessed PFS is shown in Figure 1.

Table 10: Investigator-assessed efficacy results in CLL14 (65-month follow-up)

Endpoint	**Venetoclax + obinutuzumab N = 216**	**Obinutuzumab + chlorambucil N = 216**
Progression-free survival		
Number of events (%)	80 (37)	150 (69)
Median, months (95% CI)	NR (64.8, NE)	36.4 (34.1, 41.0)
Hazard ratio, stratified (95% CI)	0.35 (0.26, 0.46)	
Overall survival		
Number of events (%)	40 (19)	57 (26)
Hazard ratio, stratified (95% CI)	0.72 (0.48, 1.09)	
CI= confidence interval; NE = not evaluable; NR = not reached		

Figure 1: Kaplan-Meier curve of investigator-assessed progression-free survival (intent-to-treat population) in CLL14 with 65-month follow-up



The PFS benefit with venetoclax + obinutuzumab versus obinutuzumab + chlorambucil treatment was observed across all subgroups of patients evaluated, including high-risk patients with deletion 17p and/or *TP53* mutation and/or unmutated *IgVH*.

Venetoclax in combination with rituximab for the treatment of patients with CLL who have received at least one prior therapy – study GO28667 (MURANO)

A randomised (1:1), multicentre, open-label phase 3 study evaluated the efficacy and safety of venetoclax + rituximab versus bendamustine + rituximab in patients with previously treated CLL. Patients in the venetoclax + rituximab arm completed the Venclyxto 5-week dose-titration schedule and then received 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week dose-titration schedule at 375 mg/m^2 for Cycle 1 and 500 mg/m^2 for Cycles 2-6. Each cycle was 28 days. Patients randomised to bendamustine + rituximab received bendamustine at 70 mg/m^2 on Days 1 and 2 for 6 cycles and rituximab as described above.

Median age was 65 years (range: 22 to 85); 74% were male, and 97% were white. Median time since diagnosis was 6.7 years (range: 0.3 to 29.5). Median prior lines of therapy was 1 (range: 1 to 5); and included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%) and prior purine analogues (81%, including 55% fludarabine + cyclophosphamide + rituximab (FCR)). At baseline, 47% of patients had one or more nodes ≥5 cm, and 68% had ALC ≥25 x 10^9/l. A 17p deletion was detected in 27% of patients, *TP53* mutations in 26%, 11q deletion in 37%, and unmutated *IgVH* gene in 68%. Median follow-up time for primary analysis was 23.8 months (range: 0.0 to 37.4 months).

Progression-free survival was assessed by investigators using the IWCLL updated NCI-WG guidelines (2008).

At the time of the primary analysis (data cut-off date 8 May 2017), 16% (32/194) of patients in the venetoclax + rituximab arm had experienced a PFS event, compared with 58% (114/195) in the bendamustine + rituximab arm (HR: 0.17 [95% CI: 0.11, 0.25]; p<0.0001, stratified log-rank test). The PFS events included 21 disease progression and 11 death events in the venetoclax + rituximab arm, and 98 disease progression and 16 death events in the bendamustine + rituximab arm. Median PFS

was not reached in the venetoclax + rituximab arm and was 17.0 months (95% CI: 15.5, 21.6) in the bendamustine + rituximab arm.

The 12- and 24-month PFS estimates were 93% (95% CI: 89.1, 96.4) and 85% (95% CI: 79.1, 90.6) in the venetoclax + rituximab arm and 73% (95% CI: 65.9, 79.1) and 36% (95% CI: 28.5, 44.0) in the bendamustine + rituximab arm, respectively.

Efficacy results for the primary analysis were also assessed by an IRC demonstrating a statistically significant 81% reduction in the risk of progression or death for patients treated with venetoclax + rituximab (HR: 0.19 [95% CI: 0.13, 0.28]; p<0.0001).

Investigator-assessed ORR for patients treated with venetoclax + rituximab was 93% (95% CI: 88.8, 96.4), with a CR + CRi rate of 27%, nodular partial remission (nPR) rate of 3%, and PR rate of 63%. For patients treated with bendamustine + rituximab, ORR was 68% (95% CI: 60.6, 74.2), with a CR + CRi rate of 8%, nPR rate of 6%, and PR rate of 53%. Median duration of response (DOR) was not reached with median follow-up of approximately 23.8 months. The IRC-assessed ORR for patients treated with venetoclax + rituximab was 92% (95% CI: 87.6, 95.6), with a CR + CRi rate of 8%, nPR rate of 2%, and PR rate of 82%. For patients treated with bendamustine + rituximab, IRC-assessed ORR was 72% (95% CI: 65.5, 78.5), with a CR + CRi rate of 4%, nPR rate of 1%, and PR rate of 68%. The discrepancy between IRC- and investigator-assessed CR rates was due to interpretation of residual adenopathy on CT scans. Eighteen patients in the venetoclax + rituximab arm and 3 patients in the bendamustine + rituximab arm had negative bone marrow and lymph nodes <2 cm.

MRD at the end of combination treatment was evaluated using ASO-PCR and/or flow cytometry. MRD negativity was defined as less than one CLL cell per 10^4 leukocytes. MRD negativity rates in peripheral blood were 62% (95% CI: 55.2, 69.2) in the venetoclax + rituximab arm compared to 13% (95% CI: 8.9, 18.9) in the bendamustine + rituximab arm. Of those with MRD assay results available in peripheral blood, 72% (121/167) in the venetoclax + rituximab arm and 20% (26/128) in the bendamustine + rituximab arm were found to be MRD negative. MRD negativity rates in the bone marrow were 16% (95% CI: 10.7, 21.3) in the venetoclax + rituximab arm and 1% (95% CI: 0.1, 3.7) in the bendamustine + rituximab arm. Of those with MRD assay results available in bone marrow, 77% (30/39) in the venetoclax + rituximab arm and 7% (2/30) in the bendamustine + rituximab arm were found to be MRD negative.

Median OS had not been reached in either treatment arm. Death occurred in 8% (15/194) of patients treated with venetoclax + rituximab and 14% (27/195) of patients treated with bendamustine + rituximab (hazard ratio: 0.48 [95% CI: 0.25, 0.90]).

By the data cut-off date, 12% (23/194) of patients in the venetoclax + rituximab arm and 43% (83/195) of patients in the bendamustine + rituximab arm had started a new anti-leukaemic treatment or died (stratified hazard ratio: 0.19; [95% CI: 0.12, 0.31]). The median time to new anti-leukaemic treatment or death was not reached in the venetoclax + rituximab arm and was 26.4 months in the bendamustine + rituximab arm.

59-month follow-up

Efficacy was assessed after a median follow-up of 59 months (data cut-off date 8 May 2020). Efficacy results for the MURANO 59-month follow-up are presented in Table 11.

Table 11: Investigator-assessed efficacy results in MURANO (59-month follow-up)

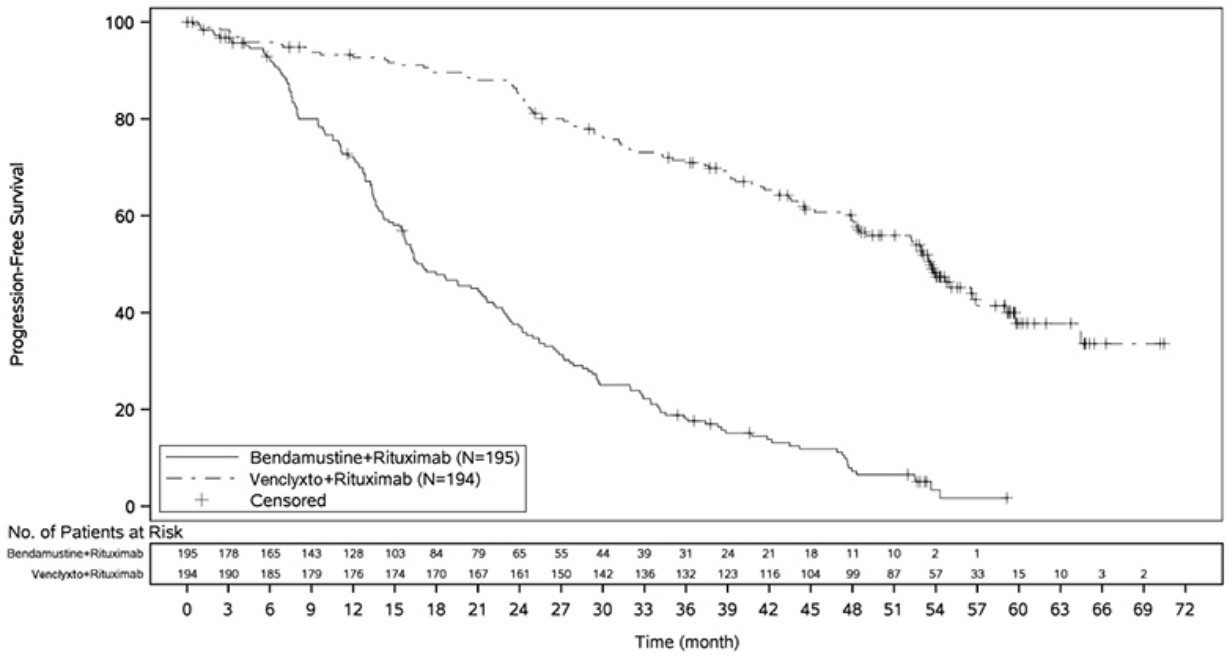
Endpoint	**Venetoclax + rituximab N = 194**	**Bendamustine + rituximab N = 195**
Progression-free survival		
Number of events (%)[a]	101 (52)	167 (86)
Median, months (95% CI)	54 (48.4, 57.0)	17 (15.5, 21.7)
Hazard ratio, stratified (95% CI)	0.19 (0.15, 0.26)	
Overall survival		
Number of events (%)	32 (16)	64 (33)
Hazard ratio (95% CI)	0.40 (0.26, 0.62)	
60-month estimate, % (95% CI)	82 (76.4, 87.8)	62 (54.8, 69.6)
Time to next anti-leukaemic treatment		
Number of events (%)[b]	89 (46)	149 (76)
Median, months (95% CI)	58 (55.1, NE)	24 (20.7, 29.5)
Hazard ratio, stratified (95% CI)	0.26 (0.20, 0.35)	
MRD negativity[c]		
Peripheral blood at end of treatment, n (%)[d]	83 (64)	NA[f]
3-year PFS estimate from end of treatment, % (95% CI)[e]	61 (47.3, 75.2)	NA[f]
3-year OS estimate from end of treatment, % (95% CI)[e]	95 (90.0, 100.0)	NA[f]

CI= confidence interval; MRD = minimal residual disease; NE = not evaluable; OS= overall survival; PFS = progression-free survival; NA = not applicable.
[a]87 and 14 events in the venetoclax + rituximab arm were due to disease progression and death, compared to 148 and 19 events in the bendamustine + rituximab arm, respectively.
[b]68 and 21 events in the venetoclax + rituximab arm were due to patients starting a new anti-leukaemic treatment and death, compared to 123 and 26 events in the bendamustine + rituximab arm, respectively.
[c]Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry. The cut-off for a negative status was one CLL cell per 10^4 leukocytes.
[d]In patients who completed venetoclax treatment without progression (130 patients).
[e]In patients who completed venetoclax treatment without progression and were MRD negative (83 patients).
[f]No equivalent to end of treatment visit in bendamustine + rituximab arm.

In total, 130 patients in the venetoclax + rituximab arm completed 2 years of venetoclax treatment without progression. For these patients, the 3-year PFS estimate post-treatment was 51% (95 % CI: 40.2, 61.9).

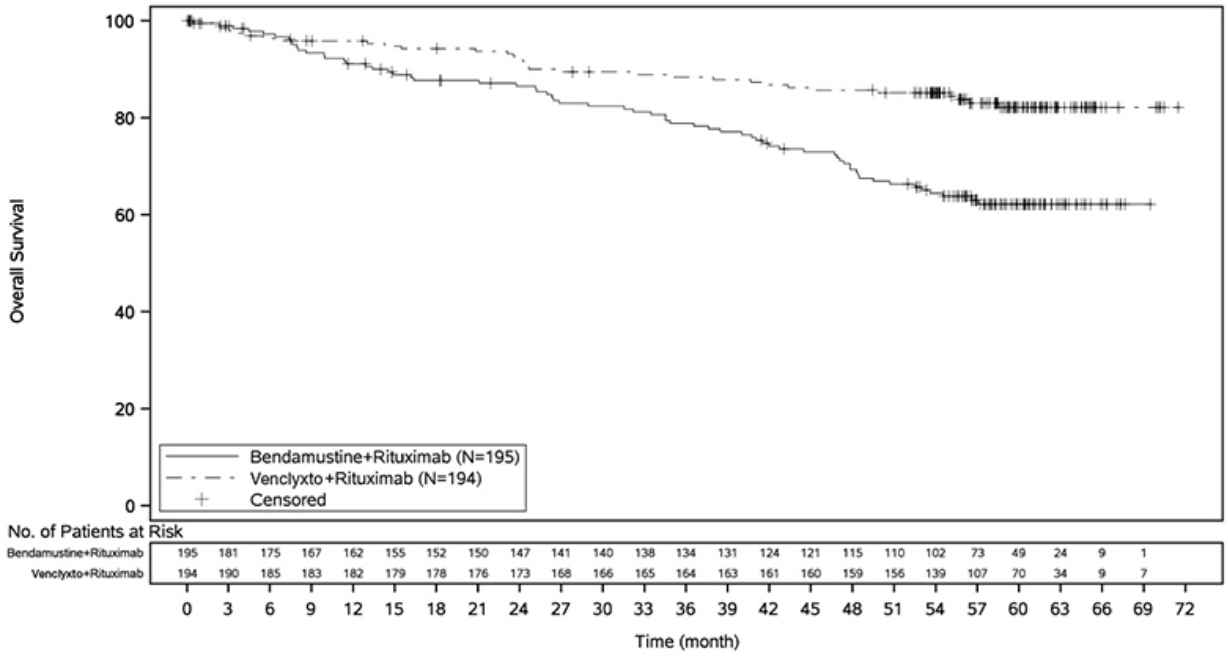
The Kaplan-Meier curve of investigator-assessed PFS is shown in Figure 2.

Figure 2: Kaplan-Meier curve of investigator-assessed progression-free survival (intent-to-treat population) in MURANO (data cut-off date 8 May 2020) with 59-month follow-up



The Kaplan-Meier curve of overall survival is shown in Figure 3.

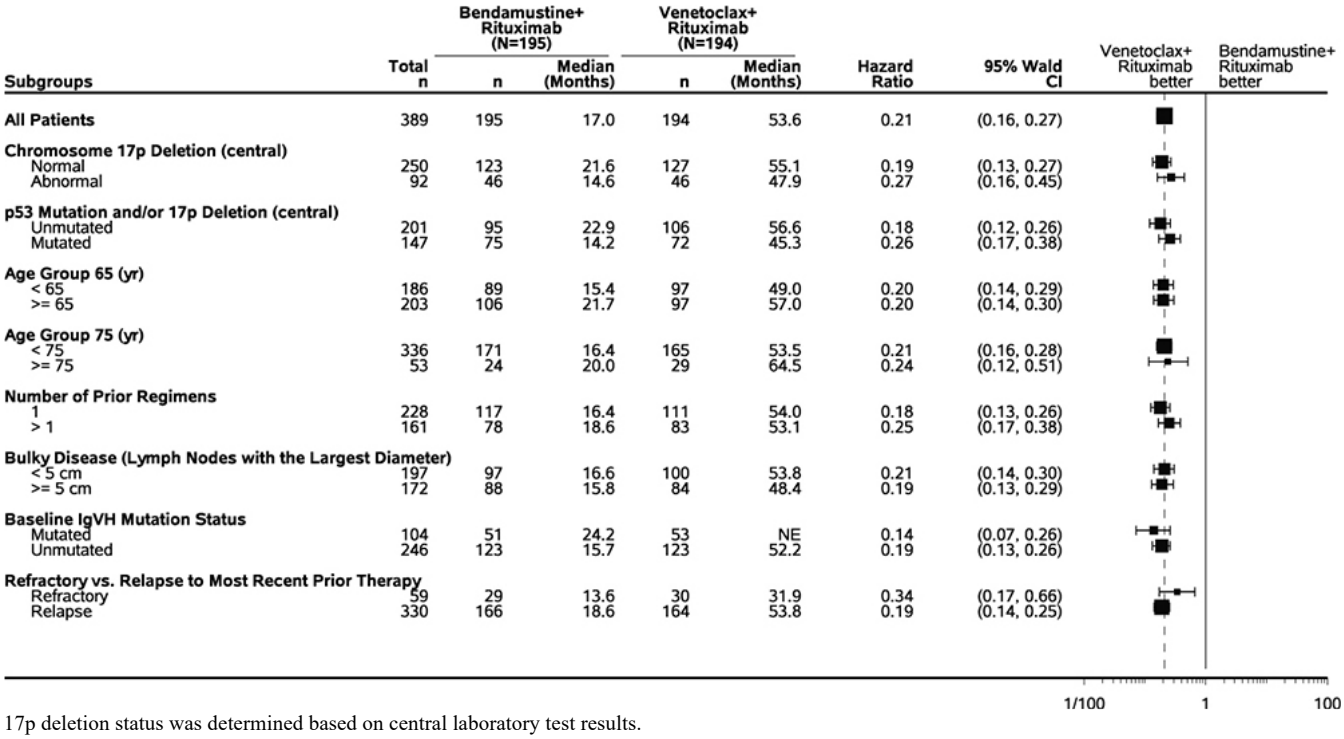
Figure 3: Kaplan-Meier curve of overall survival (intent-to-treat population) in MURANO (data cut-off date 8 May 2020) with 59-month follow-up



Results of subgroup analyses

The observed PFS benefit of venetoclax + rituximab compared with bendamustine + rituximab was consistently observed across all subgroups of patients evaluated, including high-risk patients with deletion 17p/*TP53* mutation and/or unmutated *IgVH* (Figure 4).

Figure 4: Forest plot of investigator-assessed progression-free survival in subgroups from MURANO (data cut-off date 8 May 2020) with 59-month follow-up



17p deletion status was determined based on central laboratory test results.
Unstratified hazard ratio is displayed on the X-axis with logarithmic scale.
NE=not evaluable.

Venetoclax as monotherapy for the treatment of patients with CLL harbouring 17p deletion or TP53 mutation – study M13-982

The safety and efficacy of venetoclax in 107 patients with previously treated CLL with 17p deletion were evaluated in a single-arm, open-label, multicentre 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 venetoclax 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 ≥5 cm, and 51% had ALC ≥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 ORR as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008). Efficacy results are shown in Table 12. 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 results 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 12: Efficacy results in patients with previously treated CLL with 17p deletion (study M13-982)

Endpoint	IRC assessment (N = 107)[a]	Investigator assessment (N = 158)[b]
Data cutoff 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; DOR = duration of response; IRC = independent review committee; nPR = nodular PR; NA = not available; NR = not reached; ORR = overall response rate; 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 CR, CRi, or PR with limited remaining disease with venetoclax 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.

Venetoclax as monotherapy for the treatment of patients with CLL who have failed a B-cell receptor pathway inhibitor – study M14-032

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

At the time of data cut-off (26 July 2017), 127 patients were enrolled and treated with venetoclax. Of these, 91 patients had received prior ibrutinib therapy (Arm A) and 36 had received prior idelalisib therapy (Arm B). The median age was 66 years (range: 28 to 85 years), 70% were male, and 92% were white. The median time since diagnosis was 8.3 years (range: 0.3 to 18.5 years; N=96). Chromosomal aberrations were 11q deletion (34%, 43/127), 17p deletion (40%, 50/126), *TP53* mutation (38%, 26/68) and unmutated *IgVH* (78%, 72/92). At baseline, 41% of patients had one or more nodes ≥5 cm and 31% had ALC ≥25 x 10^9/l. The median number of prior oncology treatments was 4 (range: 1 to 15) in ibrutinib-treated patients and 3 (range: 1 to 11) in idelalisib-treated patients. Overall, 65% of patients received prior nucleoside analogue, 86% rituximab, 39% other monoclonal antibodies, and 72% alkylating agent (including 41% with bendamustine). At the time of evaluation, median duration of treatment with venetoclax was 14.3 months (range: 0.1 to 31.4 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 13: Efficacy results as assessed by investigator in patients who have failed a B-cell receptor pathway inhibitor (study M14-032)

Endpoint	**Arm A (ibrutinib failures) (N = 91)**	**Arm B (idelalisib failures) (N = 36)**	**Total (N = 127)**
ORR, % (95% CI)	65 (54.1, 74.6)	67 (49.0, 81.4)	65 (56.4, 73.6)
CR + CRi, %	10	11	10
nPR, %	3	0	2
PR, %	52	56	53
PFS, % (95% CI) 12-month estimate 24-month estimate	 75 (64.7, 83.2) 51 (36.3, 63.9)	 80 (63.1, 90.1) 61 (39.6, 77.4)	 77 (68.1, 83.4) 54 (41.8, 64.6)
PFS, months, median (95% CI)	25 (19.2, NR)	NR (16.4, NR)	25 (19.6, NR)
OS, % (95% CI) 12-month estimate	 91 (82.8, 95.4)	 94.2 (78.6, 98.5)	 92 (85.6, 95.6)
TTR, months, median (range)	2.5 (1.6-14.9)	2.5 (1.6-8.1)	2.5 (1.6-14.9)
17p deletion and/or *TP53* mutation status ORR, % (95% CI)			
Yes	(n=28) 61 (45.4, 74.9)	(n=7) 58 (27.7, 84.8)	(n=35) 60 (46.6, 73.0)
No	(n=31) 69 (53.4, 81.8)	(n=17) 71 (48.9, 87.4)	(n=48) 70 (57.3, 80.1)
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; nPR = nodular PR; NR = not reached, ORR = overall response rate; OS = overall survival; PFS = progression-free survival, PR = partial remission, TTR = time to first response.			

The efficacy data were further evaluated by an IRC demonstrating a combined ORR of 70% (Arm A: 70%; Arm B: 69%). One patient (ibrutinib failure) achieved CRi. The ORR for patients with 17p deletion and/or *TP53* mutation was 72% (33/46) (95% CI: 56.5, 84.0) in Arm A and 67% (8/12) (95% CI: 34.9, 90.1) in Arm B. For patients without 17p deletion and/or *TP53* mutation, the ORR was 69% (31/45) (95% CI: 53.4, 81.8) in Arm A and 71% (17/24) (95% CI: 48.9, 87.4) in Arm B.

Median OS and DOR were not reached with median follow-up of approximately 14.3 months for Arm A and 14.7 months for Arm B.

Twenty-five percent (32/127) of patients were MRD negative in the peripheral blood, including 8 patients who were also MRD negative in bone marrow.

Acute myeloid leukaemia

Venetoclax was studied in adult patients who were ≥ 75 years of age, or who had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2–3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance (CrCl) < 45 ml/min, or other comorbidity.

Venetoclax in combination with azacitidine for the treatment of patients with newly diagnosed AML - study M15-656 (VIALE-A)

VIALE-A was a randomised (2:1), double-blind, placebo-controlled phase 3 study that evaluated the efficacy and safety of venetoclax in combination with azacitidine in patients with newly diagnosed AML who were ineligible for intensive chemotherapy.

Patients in VIALE-A completed the 3-day daily titration schedule to a final 400 mg once daily dose during the first 28-day cycle of treatment (see section 4.2) and received venetoclax 400 mg orally once daily thereafter in subsequent cycles. Azacitidine at 75 mg/m^2 was administered either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. During the titration, patients received TLS prophylaxis and were hospitalised for monitoring. Once bone marrow assessment confirmed a remission, defined as less than 5% leukaemia blasts with grade 4 cytopenia following Cycle 1 treatment, venetoclax or placebo was interrupted up to 14 days or until ANC ≥500/microlitre and platelet count ≥50 × 10^3/microlitre. For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated. Azacitidine was resumed on the same day as venetoclax or placebo following interruption (see section 4.2). Azacitidine dose reduction was implemented in the clinical study for management of hematologic toxicity (see azacitidine Summary of Product Characteristics). Patients continued to receive treatment cycles until disease progression or unacceptable toxicity.

A total of 431 patients were randomised: 286 to the venetoclax + azacitidine arm and 145 to the placebo + azacitidine arm. Baseline demographic and disease characteristics were similar between the venetoclax + azacitidine and placebo + azacitidine arms. Overall, the median age was 76 years (range: 49 to 91 years), 76% were white, 60% were males, and ECOG performance status at baseline was 0 or 1 for 55% of patients, 2 for 40% of patients, and 3 for 5% of patients. There were 75% of patients with *de novo* AML and 25% with secondary AML. At baseline, 29% of patients had bone marrow blast count <30%, 22% of patients had bone marrow blast count ≥30% to <50%, and 49% had ≥50%. Intermediate or poor cytogenetic risk was present in 63% and 37% patients, respectively. The following mutations were identified: *TP53* mutations in 21% (52/249), *IDH1* and/or *IDH2* mutation in 24% (89/372), 9% (34/372) with *IDH1,* 16% (58/372) with *IDH2*, 16% (51/314) with *FLT3*, and 18% (44/249) with *NPM1*.

The primary efficacy endpoints of the study were overall survival (OS), measured from the date of randomisation to death from any cause and composite CR rate (complete remission + complete remission with incomplete blood count recovery [CR+CRi]). The overall median follow-up at the time of analysis was 20.5 months (range: <0.1 to 30.7 months).

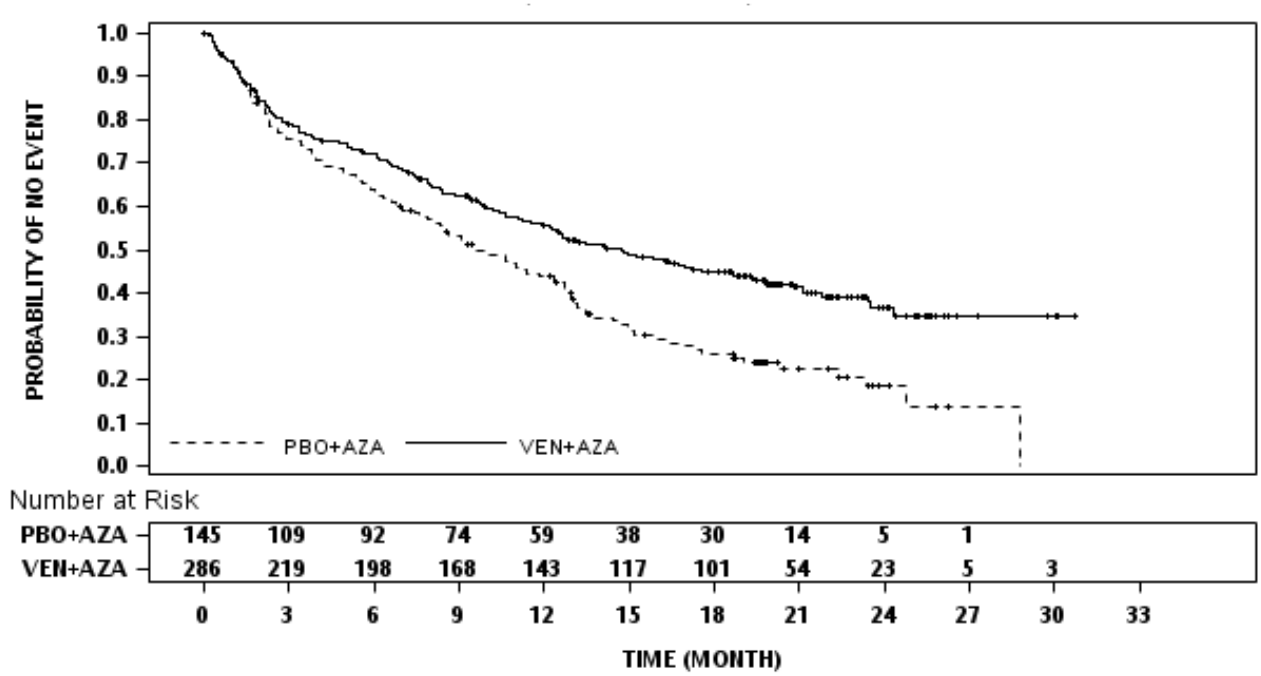
Venetoclax + azacitidine demonstrated a 34% reduction in the risk of death compared with placebo + azacitidine (p <0.001). Results are shown in Table 14.

Table 14: Efficacy results in VIALE-A

Endpoint	**Venetoclax + azacitidine**	**Placebo + azacitidine**
Overall survival[a]	(N=286)	(N=145)
Number of events n (%)	161 (56)	109 (75)
Median survival, months (95% CI)	14.7 (11.9, 18.7)	9.6 (7.4, 12.7)
Hazard ratio[b] (95% CI)	0.66 (0.52, 0.85)	
p-value[b]	<0.001	
CR+CRi rate[c]	(N=147)	(N=79)
n (%) (95% CI)	96 (65) (57, 73)	20 (25) (16, 36)
p-value[d]	<0.001	

CI = confidence interval; CR = (complete remission) was defined as absolute neutrophil count >1,000/microlitre, platelets >100,000/microlitre, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; CRi = complete remission with incomplete blood count recovery.
[a]Kaplan-Meier estimate at the second interim analysis (data cut-off date 4 January 2020).
[b]Hazard ratio estimate (venetoclax +azacitidine vs. placebo + azacitidine) is based on Cox-proportional hazards model stratified by cytogenetics (intermediate risk, poor risk) and age (18to <75, ≥75) as assigned at randomisation; p-value based on log-rank test stratified by the same factors.
[c]The CR+CRi rate is from a planned interim analysis of first 226 patients randomised with 6 months of follow-up at the first interim analysis (data cut-off date 1 October 2018).
[d]P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75, ≥75) and cytogenetic risk (intermediate risk, poor risk) as assigned at randomisation.

Figure 5: Kaplan-Meier curve for overall survival in VIALE-A



Key secondary efficacy endpoints are presented in Table 15.

Table 15: Additional efficacy endpoints in VIALE-A

Endpoint	**Venetoclax + azacitidine N=286**	**Placebo + azacitidine N=145**
CR rate		
n (%)	105 (37)	26 (18)
(95% CI)	(31, 43)	(12, 25)
p-value[a]	<0.001	
Median DOR[b], months	17.5	13.3
(95% CI)	(15.3, -)	(8.5, 17.6)
CR+CRi rate		
n (%)	190 (66)	41(28)
(95% CI)	(61, 72)	(21, 36)
Median DOR[b], months	17.5	13.4
(95% CI)	(13.6, -)	(5.8, 15.5)

CR+CRi rate by initiation of Cycle 2, n (%) (95% CI)	124 (43) (38, 49)	11 (8) (4, 13)
p-value[a]	<0.001	
Transfusion independence rate, platelets n (%) (95% CI)	196 (69) (63, 74)	72 (50) (41, 58)
p-value[a]	<0.001	
Transfusion independence rate, red blood cells n (%) (95% CI)	171 (60) (54, 66)	51 (35) (27, 44)
p-value[a]	<0.001	
CR+CRi MRD response rate[d] n (%) (95% CI)	67 (23) (19, 29)	11 (8) (4, 13)
p-value[a]	<0.001	
Event-free survival Number of events, n (%) Median EFS[e], months (95% CI)	191 (67) 9.8 (8.4, 11.8)	122 (84) 7.0 (5.6, 9.5)
Hazard ratio (95% CI)[c]	0.63 (0.50, 0.80)	
p-value[c]	<0.001	

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; DOR = duration of response; EFS = event-free survival; MRD = minimal/measurable residual disease; n = number of responses or number of events; - = not reached.

CR (complete remission) was defined as absolute neutrophil count >1,000/microlitre, platelets >100,000/microlitre, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.

Transfusion independence was defined as a period of at least consecutive 56 days (≥56 days) with no transfusion after the first dose of study drug and on or before the last dose of the study drug + 30 days, or before relapse or disease progression or before the initiation of post treatment therapy whichever is earlier.

[a]P-value is from Cochran-Mantel-Haenszel test stratified by age (18 to <75, ≥75) and cytogenetic risk (intermediate risk, poor risk) as assigned at randomisation.
[b]DOR (duration of response) was defined as time from first response of CR for DOR of CR, from first response of CR or CRi for DOR of CR+CRi, to the first date of confirmed morphologic relapse, confirmed progressive disease or death due to disease progression, whichever occurred earlier. Median DOR is from Kaplan-Meier estimate.
[c]Hazard ratio estimate (venetoclax + azacitidine vs. placebo + azacitidine) is based on Cox-proportional hazards model stratified by age (18 to <75, ≥75) and cytogenetics (intermediate risk, poor risk) as assigned at randomisation; p-value based on log-rank test stratified by the same factors.
[d] CR+CRi MRD response rate is defined as the % of patients achieving a CR or CRi and demonstrated an MRD response of $<10^{-3}$ blasts in bone marrow as determined by a standardized, central multicolour flow cytometry assay.
[e]Kaplan-Meier estimate.

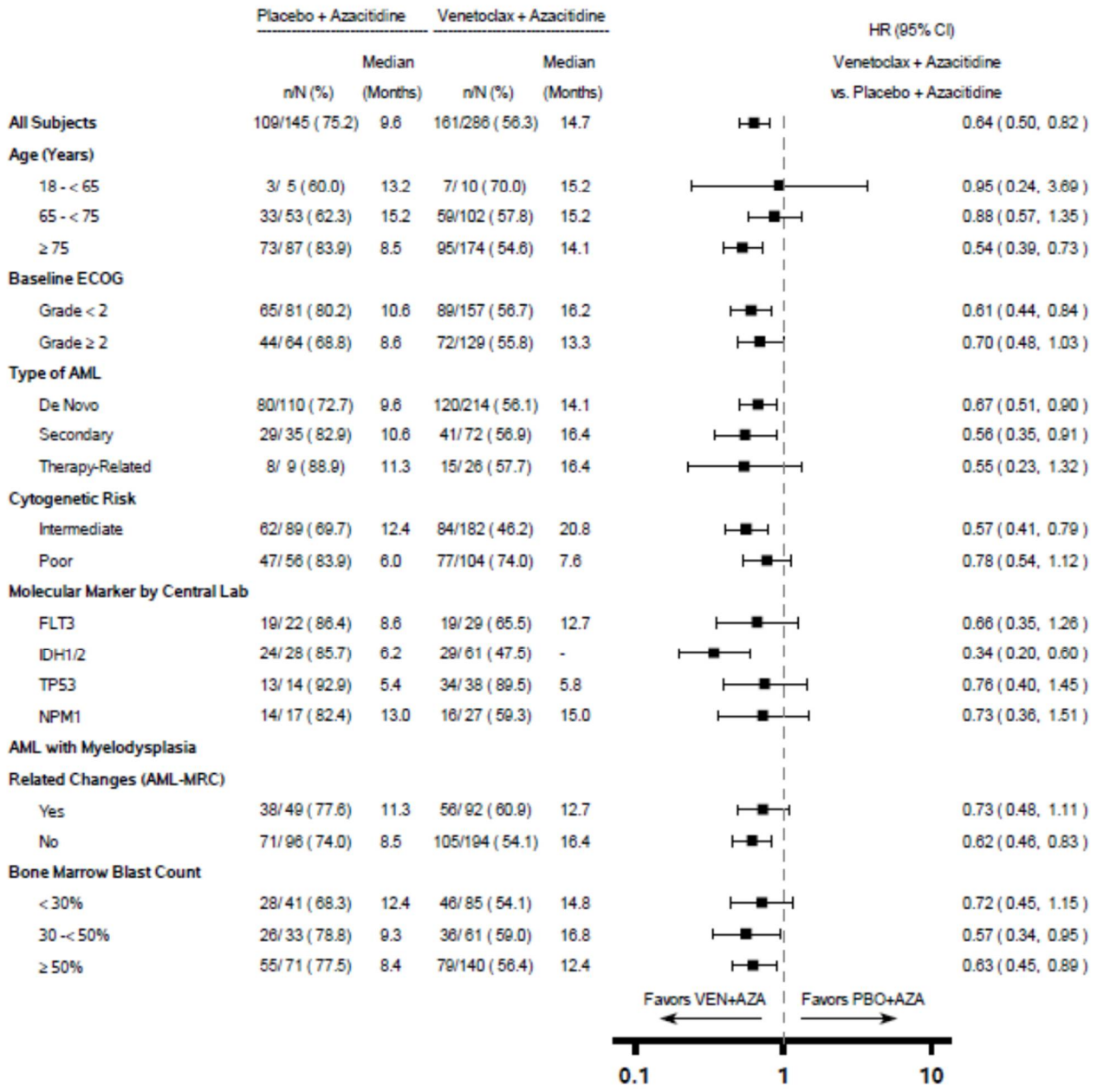
Of patients with the *FLT3* mutation, the CR+CRi rates were 72% (21/29; [95% CI: 53, 87]) and 36% (8/22; [95% CI: 17, 59]) in the venetoclax + azacitidine and placebo + azacitidine arms, respectively (p=0.021).

Of patients with *IDH1/IDH2* mutations, the CR+CRi rates were 75% (46/61; [95% CI: 63, 86]) and 11% (3/28; [95% CI: 2, 28]) in the venetoclax + azacitidine and placebo + azacitidine arms, respectively ($p<0.001$).

Of the patients who were RBC transfusion dependent at baseline and treated with venetoclax + azacitidine, 49% (71/144) became transfusion independent. Of the patients who were platelet transfusion dependent at baseline and treated with venetoclax + azacitidine, 50% (34/68) became transfusion independent.

The median time to first response of CR or CRi was 1.3 months (range: 0.6 to 9.9 months) with venetoclax + azacitidine treatment. The median time to best response of CR or CRi was 2.3 months (range: 0.6 to 24.5 months).

Figure 6: Forest plot of overall survival by subgroups from VIALE-A



- = Not reached.

For the pre-specified secondary endpoint OS in the *IDH1/2* mutation subgroup, p<0.0001 (unstratified log-rank test).

Unstratified hazard ratio (HR) is displayed on the X-axis with logarithmic scale.

V*enetoclax in combination with azacitidine or decitabine for the treatment of patients with newly diagnosed AML - M14-358*

Study M14-358 was a non-randomised phase 1/2 clinical study of venetoclax in combination with azacitidine (n=84) or decitabine (n=31) in patients with newly diagnosed AML who were ineligible for intensive chemotherapy. Patients received venetoclax via a daily titration to a final 400 mg once daily dose. The administration of azacitidine in M14-358 was similar to that of VIALE-A randomised study. Decitabine at 20 mg/m^2 was administered intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1.

The median follow-up was 40.4 months (range: 0.7 to 42.7 months) for venetoclax + decitabine.

The median age of patients treated with venetoclax + decitabine was 72 years (range: 65-86 years), 87% were white, 48% males, and 87% had ECOG score 0 or 1. The CR+CRi rate was 74% (95% CI: 55, 88) in combination with decitabine.

Elderly patients

Of the 194 patients with previously treated CLL who received venetoclax in combination with rituximab, 50% were 65 years or older.

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

Of the 127 patients who were evaluated for efficacy from M14-032 study, 58% were 65 years or older.

Of the 352 patients evaluated for safety from 3 open-label monotherapy studies, 57% were 65 years or older.

Of the 283 patients with newly diagnosed AML treated in the VIALE-A (venetoclax + azacitidine arm) clinical study, 96% were ≥65 years of age and 60% were ≥75 years of age.

Of the 31 patients treated with venetoclax in combination with decitabine in the M14-358 clinical study, 100% were ≥65 years of age and 26% were ≥75 years of age.

There were no clinically meaningful differences in safety or efficacy observed between older and younger patients in the combination and monotherapy studies.

Paediatric population

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

The European Medicines Agency has deferred the obligation to submit the results of studies with Venclyxto in one or more subsets of the paediatric population in AML (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

Effect of food

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

Distribution

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 micromolar (0.87-26 mcg/ml). The mean blood-to-plasma ratio was 0.57.

The population estimate for apparent volume of distribution (Vd_{ss}/F) of venetoclax ranged from 256-321 L in patients.

Biotransformation

In vitro studies demonstrated that venetoclax 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 venetoclax *in vitro*.

In vitro interaction studies

Co-administration with CYP and UGT substrates

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

Co-administration with transporter substrates/inhibitors

Venetoclax 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). Venetoclax 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 venetoclax was approximately 26 hours. Venetoclax shows minimal accumulation with accumulation ratio of 1.30-1.44. After a single oral administration of 200 mg radiolabeled [^{14}C]-venetoclax 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 venetoclax accounted for 20.8% of the administered radioactive dose excreted in faeces. The pharmacokinetics of venetoclax do not change over time.

Special populations

Renal impairment

Based on a population pharmacokinetic analysis that included 321 subjects with mild renal impairment (CrCl ≥60 and <90 ml/min), 219 subjects with moderate renal impairment (CrCl ≥30 and <60 ml/min), 5 subjects with severe renal impairment (CrCl ≥15 and <30 ml/min) and 224 subjects with normal renal function (CrCl ≥90 ml/min), venetoclax exposures in subjects with mild, moderate or severe renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with CrCl <15 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, venetoclax 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.

In a dedicated hepatic impairment study, venetoclax C_{max} and AUC in subjects with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=6) hepatic impairment were similar to subjects with normal hepatic function, after receiving a 50 mg single dose of venetoclax. In subjects with severe

(Child-Pugh C; n=5) hepatic impairment, the mean venetoclax C_{max} was similar to subjects with normal hepatic function but venetoclax AUC_{inf} was on average 2.7-fold higher (range: no change to 5-fold higher) than venetoclax AUC_{inf} in the subjects with normal hepatic function (see section 4.2).

Effects of age, sex, weight and race

Based on population pharmacokinetic analyses, age, sex, and weight do not have an effect on venetoclax clearance. The exposure is 67% higher in Asian subjects as compared to non-Asian subjects. This difference is not considered clinically relevant.

5.3 Preclinical safety data

Toxicities observed in animal studies with venetoclax included dose-dependent reductions in lymphocytes and red blood cell mass. Both effects were reversible after cessation of dosing with venetoclax, 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.

Venetoclax 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, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment in the hair.

Carcinogenicity/genotoxicity

Venetoclax and the M27 major human metabolite were not carcinogenic in a 6-month transgenic (Tg.rasH2) mouse carcinogenicity study at oral doses up to 400 mg/kg/day of venetoclax and at a single dose level of 250 mg/kg/day of M27. Exposure margins (AUC), relative to the clinical AUC at 400 mg/day, were approximately 2-fold for venetoclax and 5.8-fold for M27.

Venetoclax 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 a dose of 400 mg. Reversibility of this finding has not been demonstrated.

In embryo-foetal development studies in mice, venetoclax was associated with increased post-implantation loss and decreased foetal body weight at exposures of 1.1 times the human AUC exposure at a dose of 400 mg. The major human metabolite M27 was associated with post-implantation loss and resorptions at exposures approximately 9-times the human M27-AUC exposure at a 400 mg dose of venetoclax. In rabbits, venetoclax produced maternal toxicity, but no foetal toxicity at exposures of 0.1 times the human AUC exposure at a 400 mg dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Venclyxto 10 mg film-coated tablets

Tablet core

Copovidone (K 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)

Venclyxto 50 mg film-coated tablets

Tablet core

Copovidone (K 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)

Venclyxto 100 mg film-coated tablets

Tablet core

Copovidone (K 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

Venclyxto 10 mg film-coated tablets
2 years.

Venclyxto 50 mg film-coated tablets
2 years.

Venclyxto 100 mg film-coated tablets
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

Venclyxto film-coated tablets are supplied in PVC/PE/PCTFE aluminium foil blisters containing either 1, 2 or 4 film-coated tablets.

Venclyxto 10 mg film-coated tablets
The film-coated tablets are supplied in cartons containing either 10 or 14 tablets (in blisters of 2 tablets).

Venclyxto 50 mg film-coated tablets
The film-coated tablets are supplied in cartons containing either 5 or 7 tablets (in blisters of 1 tablet).

Venclyxto 100 mg film-coated tablets
The film-coated tablets are supplied in cartons containing either 7 (in blisters of 1 tablet) or 14 tablets (in blisters of 2 tablets); or a multipack containing 112 tablets (4 x 28 tablets (in blisters of 4 tablets)).

Not all pack sizes may be marketed.

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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/001 (10 mg, 10 tablets)
EU/1/16/1138/002 (10 mg, 14 tablets)
EU/1/16/1138/003 (50 mg, 5 tablets)
EU/1/16/1138/004 (50 mg, 7 tablets)
EU/1/16/1138/005 (100 mg 7 tablets)
EU/1/16/1138/006 (100 mg, 14 tablets)
EU/1/16/1138/007 (100 mg, 112 (4 x 28) tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 December 2016
Date of latest renewal: 6 September 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of Venclyxto in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at:

- Informing haematologists on the risk of TLS, strict adherence to dose-titration schedule and TLS risk minimisation measures for Venclyxto in the updated SmPC.
- Informing haematologists to provide each patient with the patient card, which includes a list of symptoms of TLS to prompt patient actions including to seek immediate medical attention in case of their occurrence, and patient behaviours to prevent TLS.

The MAH shall ensure that in each Member State where Venclyxto is marketed, all healthcare professionals (HCPs) and patients/carers who are expected to prescribe, dispense, or use Venclyxto have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:
- The Summary of Product Characteristics
- Patient card

- **Patient card**:
  - Contact details of the venetoclax prescriber and patient
  - Instruction to patients on how to minimise TLS risk
  - List of TLS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence
  - Instructions that the patient should carry the patient card at all times and to share it with HCPs involved in their care (i.e., urgent care HCPs, etc.)
  - Information for the HCPs treating the patient that venetoclax treatment is associated with the risk of TLS.

The patient information pack:
- Package leaflet

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER CARTON

CARTON (5 day pack)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER CARTON

CARTON (7 day pack)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg tablets
venetoclax

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER CARTON

CARTON (5 day pack)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 50 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

5 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER CARTON

CARTON (7 day pack)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 50 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 50 mg tablets
venetoclax

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER CARTON

CARTON (7 day pack)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg tablets
venetoclax

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER CARTON

CARTON (7 day pack)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER CARTON

CARTON Multipack (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 112 (4 x 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CARTON multipack (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose at the same time each day with a meal and water.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

venclyxto 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Venclyxto 10 mg film-coated tablets
Venclyxto 50 mg film-coated tablets
Venclyxto 100 mg film-coated tablets
venetoclax

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Venclyxto is and what it is used for

What Venclyxto is
Venclyxto is a cancer medicine that contains the active substance venetoclax. It belongs to a group of medicines called "BCL-2 inhibitors".

What Venclyxto is used for
Venclyxto is used to treat adults with:
- chronic lymphocytic leukaemia (CLL). Venclyxto may be given to you in combination with other medicines or alone.
- acute myeloid leukaemia (AML). Venclyxto will be given in combination with other medicines.

CLL is a type of cancer affecting white blood cells called lymphocytes and the lymph nodes. In CLL, the lymphocytes multiply too quickly and live for too long, so that there are too many of them in the blood.

AML is a type of cancer affecting white blood cells called myeloid cells. In AML, myeloid blood cells multiply and grow very quickly in bone marrow and blood, so that there are too many of them and not enough red blood cells in the blood.

How Venclyxto works
Venclyxto works by blocking a protein in the body called "BCL-2". This protein is present in high amounts in some cancer cells and helps cancer cells survive. Blocking this protein helps to kill and lower the number of cancer cells. It also slows down the worsening of the disease.

2. What you need to know before you take Venclyxto

Do not take Venclyxto if:
- you are allergic to the active substance venetoclax or any of the other ingredients of this medicine (listed in section 6).

- you have CLL and are taking any of the medicines listed below when you start your treatment and while your dose is gradually being increased (usually over 5 weeks). This is because serious and life-threatening effects can occur when Venclyxto is taken with these medicines:

    - itraconazole ketoconazole, posaconazole, or voriconazole for fungal infections
    - clarithromycin for bacterial infections
    - ritonavir for HIV infection.

  When your Venclyxto dose has been increased to the full standard dose, check with your doctor if you can start taking these medicines again.

- you are taking a herbal medicine called St. John's wort, used for depression. If you are not sure about this, talk to your doctor, pharmacist or nurse before taking Venclyxto.

It is important that you tell your doctor, pharmacist, or nurse about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Your doctor may need to stop certain medicines when you first start taking Venclyxto and during the first days or weeks when your dose is increased to the full standard dose.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Venclyxto if:

- you have any kidney problems as your risk for a side effect called tumour lysis syndrome may increase
- you have liver problems as this may increase your risk for side effects. Your doctor may need to reduce your dose of Venclyxto
- you think you may have an infection or have had a long-lasting or repeated infection
- you are due to have a vaccine.

If any of the above apply to you, or you are not sure, talk to your doctor, pharmacist, or nurse before taking this medicine.

Tumour Lysis Syndrome
Some people may develop unusual levels of some body salts (such as potassium and uric acid) in the blood caused by the fast breakdown of cancer cells during treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. This is called tumour lysis syndrome (TLS). The risk for TLS is in the first days or weeks of treatment with Venclyxto, as you increase your dose.

If you have CLL
Your doctor, pharmacist or nurse will do blood tests to check for TLS.

Your doctor will also give you medicines to help prevent the build-up of uric acid in your body before you start treatment with Venclyxto.

Drinking plenty of water, at least 1.5 to 2 litres per day, helps to remove cancer cell breakdown products from your body through urine and may decrease your risk of getting TLS (see section 3).

Tell your doctor, pharmacist or nurse immediately if you get any of the symptoms of TLS listed in section 4.

If you are at risk of TLS you may be treated in hospital so that you can be given fluids into the vein if needed, have blood tests done more often and to check for side effects. This is to see if you can continue to take this medicine safely.

If you have AML
You may be treated in hospital and your doctor or nurse will make sure that you have enough water/fluids, give you medicines to prevent the build-up of uric acid in your body and do blood tests before you start to take Venclyxto, while they increase your dose and when you start to take the full dose.

Children and adolescents
Venclyxto should not be used in children and adolescents. This is because it has not been studied in these age groups.

Other medicines and Venclyxto
Tell your doctor or pharmacist if you take any of the following medicines as they can increase or decrease the amount of venetoclax in your blood:

- medicines for fungal infections – fluconazole, itraconazole, ketoconazole, posaconazole, or voriconazole
- antibiotics to treat bacterial infections – ciprofloxacin, clarithromycin, erythromycin, nafcillin, or rifampicin
- medicines to prevent seizures or to treat epilepsy – carbamazepine, phenytoin
- medicines for HIV infection – efavirenz, etravirine, ritonavir
- medicines to treat raised blood pressure or angina – diltiazem, verapamil
- medicines to lower cholesterol levels in the blood – cholestyramine, colestipol, colesevelam
- a medicine used to treat a lung condition called pulmonary arterial hypertension – bosentan
- a medicine to treat sleep disorder (narcolepsy) known as modafinil
- a herbal medicine known as St. John's wort

Your doctor may change your dose of Venclyxto.

Tell your doctor if you take any of the following medicines as Venclyxto may affect how they work:

- medicines that prevent blood clots, warfarin, dabigatran
- a medicine used to treat heart problems known as digoxin
- a medicine for cancer known as everolimus
- a medicine used to prevent organ rejection known as sirolimus
- medicines to lower cholesterol levels in the blood known as statins

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because Venclyxto may affect the way some other medicines work. Also, some other medicines can affect the way Venclyxto works.

Venclyxto with food and drink
Do not eat grapefruit products, Seville oranges (bitter oranges, often used in marmalades), or starfruit (carambola) while you are taking Venclyxto – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because they can increase the amount of venetoclax in your blood.

Pregnancy
- Do not get pregnant while you are taking this medicine. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before taking this medicine.
- Venclyxto should not be used during pregnancy. There is no information about the safety of venetoclax in pregnant women.

Contraception
- Women of childbearing age must use a highly effective method of contraception during treatment and for at least 30 days after receiving Venclyxto to avoid becoming pregnant. If you are using hormonal contraceptive pills or devices, you must also use a barrier method of contraception (such as condoms) as the effect of hormonal contraceptive pills or devices may be affected by Venclyxto.
- Tell your doctor immediately if you become pregnant while you are taking this medicine.

Breast-feeding
Do not breast-feed while you are taking this medicine. It is not known whether the active substance in Venclyxto passes into breast milk.

Fertility
Based on findings in animals, Venclyxto may cause male infertility (low or no sperm count). This may affect your ability to father a child. Ask your doctor for advice on sperm storage before starting treatment with Venclyxto.

Driving and using machines
You may feel tired or dizzy after taking Venclyxto, which may affect your ability to drive or use tools or machines. If this happens, do not drive or use any tools or machines.

Venclyxto contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

3. How to take Venclyxto

Always take this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

How much to take

If you have CLL
You will begin treatment with Venclyxto at a low-dose for 1 week. Your doctor will gradually increase the dose over the next 4 weeks to the full standard dose. For the first 4 weeks you will get a new pack each week.

- the starting dose is 20 mg (two 10 mg tablets) once a day for 7 days.
- the dose will be increased to 50 mg (one 50 mg tablet) once a day for 7 days.
- the dose will be increased to 100 mg (one 100 mg tablet) once a day for 7 days.
- the dose will be increased to 200 mg (two 100 mg tablets) once a day for 7 days.
- the dose will be increased to 400 mg (four 100 mg tablets) once a day for 7 days.
    - When you are receiving Venclyxto therapy alone, you will stay on the 400 mg daily dose, which is the standard dose, for as long as necessary.
    - When you are receiving Venclyxto therapy in combination with rituximab, you will receive the 400 mg daily dose for 24 months.
    - When you are receiving Venclyxto therapy in combination with obinutuzumab, you will receive the 400 mg daily dose for approximately 10 months.

Your dose may need to be adjusted for side effects. Your doctor will advise what your dose should be.

If you have AML
You will begin treatment with Venclyxto on a lower dose. Your doctor will gradually increase the dose each day for the first 3 days. After 3 days you will take the full standard dose. The dose (tablets) is taken once a day.

Doses are listed in the table below

Day	Venclyxto daily dose
1	100 mg (One 100 mg tablet)
2	200 mg (Two 100 mg tablets)
3 and after	400 mg (Four 100 mg tablets)

Your doctor will give you Venclyxto in combination with another medicine (azacitidine or decitabine). You will keep taking Venclyxto at the full dose until either your AML gets worse or you cannot take Venclyxto as it is causing serious side effects.

How to take Venclyxto
- Take the tablets with a meal at around the same time each day
- Swallow the tablets whole with a glass of water
- Do not chew, crush, or break the tablets
- During the first days or weeks of treatment as you increase the dose, you should take the tablets in the morning to help you follow-up with blood tests, if needed.

If you vomit after taking Venclyxto, do not take an extra dose that day. Take the next dose at the usual time the next day. If you have problems taking this medicine, talk to your doctor.

Drink plenty of water

If you have CLL
It is very important that you drink plenty of water when taking Venclyxto during the first 5 weeks of treatment. This will help to remove cancer cell breakdown products from your blood through your urine.

You should start drinking at least 1.5 to 2 litres of water daily two days before starting Venclyxto. You may also include non-alcoholic and non-caffeinated drinks in this amount, but exclude grapefruit, Seville orange, or starfruit (carambola) juices. You should continue to drink at least 1.5 to 2 litres of water on the day you start Venclyxto. Drink the same amount of water (at least 1.5 to 2 litres daily) two days before and on the day that your dose is increased.

If your doctor thinks that you are at risk of TLS, you may be treated in the hospital so that you can be given extra fluids into the vein if needed, have your blood tests more often and be checked for side effects. This is to see if you can continue to take this medicine safely.

If you have AML
It is very important you drink plenty of water when taking Venclyxto especially when you start treatment and increase your dose. Drinking water will help to remove cancer cell breakdown products from your blood through your urine. Your doctor or nurse will give you fluids into the vein if needed if you are in hospital to make sure this happens.

If you take more Venclyxto than you should
If you take more Venclyxto than you should, talk to your doctor, pharmacist, or nurse or go to hospital immediately. Take the tablets and this leaflet with you.

If you forget to take Venclyxto
- If it is less than 8 hours since the time you usually take your dose, take it as soon as possible.

- If it is more than 8 hours since the time you usually take your dose, do not take the dose that day. Return to your normal dose schedule the next day.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure talk to your doctor, pharmacist or nurse.

Do not stop taking Venclyxto
Do not stop taking this medicine unless your doctor tells you to. If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following serious side effects may happen with this medicine:

Tumour lysis syndrome (common – may affect up to 1 in 10 people)
Stop taking Venclyxto and seek medical attention immediately if you notice any of the symptoms of TLS:
- fever or chills
- feeling or being sick (nausea or vomiting)
- feeling confused
- feeling short of breath
- irregular heart beat
- dark or cloudy urine
- feeling unusually tired
- muscle pain or uncomfortable joints
- fits or seizures
- abdominal pain and distension

Low white blood cell count (neutropenia) and infections (very common – may affect more than 1 in 10 people)
Your doctor will check your blood count during treatment with Venclyxto. Low white blood cell count can increase your risk for infection. Signs may include fever, chills, feeling weak or confused, cough, pain or burning feeling when passing urine. Some infections such as pneumonia or blood infection (sepsis) can be serious and may lead to death. Tell your doctor immediately if you have signs of an infection while taking this medicine.

Tell your doctor if you notice any of the following side effects:

If you have CLL
Very common (may affect more than 1 in 10 people)
- pneumonia
- upper respiratory tract infection – signs include runny nose, sore throat or cough
- diarrhoea
- feeling or being sick (nausea or vomiting)
- constipation
- feeling tired

Blood tests may also show
- lower number of red blood cells
- lower number of white blood cells called lymphocytes
- higher level of potassium
- higher level of a body salt (electrolyte) called phosphate
- lower level of calcium

Common (may affect up to 1 in 10 people)
- severe infection in the blood (sepsis)
- urinary tract infection
- low number of white blood cells with fever (febrile neutropenia)

Blood tests may also show:
- higher level of creatinine
- higher level of urea

If you have AML
Very common (may affect more than 1 in 10 people)
- feeling or being sick (nausea or vomiting)
- diarrhoea
- mouth sores
- feeling tired or weak
- infection of lung or blood
- decreased appetite
- joint pain
- dizziness or fainting
- headache
- shortness of breath
- bleeding
- low blood pressure
- urinary tract infection
- weight loss
- pain in belly (abdominal pain)

Blood tests may also show
- lower number of platelets (thrombocytopenia)
- lower number of white blood cells with fever (febrile neutropenia)
- lower number of red blood cells (anaemia)
- higher level of total bilirubin
- low level of potassium in the blood

Common (may affect up to 1 in 10 people)
- gall stones or gall bladder infection

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Venclyxto

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Venclyxto contains

The active substance is venetoclax.
- Venclyxto 10 mg film-coated tablets: Each film-coated tablet contains 10 mg venetoclax.
- Venclyxto 50 mg film-coated tablets: Each film-coated tablet contains 50 mg venetoclax.
- Venclyxto 100 mg film-coated tablets: Each film-coated tablet contains 100 mg venetoclax.

The other ingredients are:
- In the tablet core: copovidone (K 28), polysorbate 80 (E433), colloidal anhydrous silica (E551), anydrous calcium hydrogen phosphate (E341 (ii)), sodium stearyl fumarate.

In the film-coating:
- Venclyxto 10 mg film-coated tablets: iron oxide yellow (E172), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b).
- Venclyxto 50 mg film-coated tablets: iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b)
- Venclyxto 100 mg film-coated tablets: iron oxide yellow (E172), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b).

What Venclyxto looks like and contents of the pack
Venclyxto 10 mg film-coated tablet is pale yellow, round 6 mm diameter, with V on one side and 10 on the other.
Venclyxto 50 mg film-coated tablet is beige, oblong 14 mm long, with V on one side and 50 on the other.
Venclyxto 100 mg film-coated tablet is pale yellow, oblong 17.2 mm long with V on one side and 100 on the other.

Venclyxto tablets are provided in blisters which are packed in cartons as follows:

Venclyxto 10 mg film-coated tablets:
- 10 tablets (5 blisters each with 2 tablets)
- 14 tablets (7 blisters each with 2 tablets)

Venclyxto 50 mg film-coated tablets:
- 5 tablets (5 blisters each with 1 tablet)
- 7 tablets (7 blisters each with 1 tablet)

Venclyxto 100 mg film-coated tablets:
- 7 tablets (7 blisters each with 1 tablet)
- 14 tablets (7 blisters each with 2 tablets)
- 112 (4 x 28) tablets (4 cartons of 7 blisters each with 4 tablets).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.