Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: http://www.gmc-uk.org/mobile/14327

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Venetoclax 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.

Venetoclax 10 mg film-coated tablet
Pale yellow, round biconvex shaped tablet 6 mm diameter.

Venetoclax 50 mg film-coated tablet
Beige, oblong biconvex shaped tablet 14 mm long, 8 mm wide.

Venetoclax 100 mg film-coated tablet
Pale yellow, oblong biconvex shaped tablet 17.2 mm long, 9.5 mm wide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Venetoclax is indicated for the treatment of adult patients with CLL in the absence of 17p deletion or *TP53* mutation, and who are unsuitable for or have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

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.

Posology

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

Table 1: Dose increase schedule

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

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

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

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

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter ≥5 cm or high absolute lymphocyte count [ALC ≥25 x 10^9/L]) are at greater risk of TLS when initiating venetoclax. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the 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-exisiting abnormalities corrected. The prophylaxis measures listed below should be followed. More intensive measures should be employed as overall risk increases:

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

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

Laboratory assessments:

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

Post-dose: For patients at risk of TLS, blood chemistries should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax. Electrolyte abnormalities should be corrected promptly. The next venetoclax dose should not be administered until the 24-hour blood chemistry results have been evaluated. The same monitoring schedule should be followed at each subsequent dose increase.

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

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

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

Table 2: Dose modification for TLS and other toxicities during venetoclax treatment

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

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

Dose modifications for use with CYP3A inhibitors

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase.

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

Concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation and titration doses of venetoclax should be reduced by at least 2-fold. Patients should be monitored more closely for signs of toxicities (see sections 4.4 and 4.5).

For patients who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by at least 2-fold when used concomitantly with moderate CYP3A inhibitors and by at least 4-fold when used concomitantly with strong CYP3A inhibitors. Patients should be monitored more closely for signs of toxicities. 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 4.4 and 4.5).

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

Hepatic impairment
Although no dose adjustment is recommended in patients with mild or moderate hepatic impairment based on the results of population pharmacokinetic analysis, a trend for increased adverse events was observed in patients with moderate hepatic impairment; these patients should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase (see section 4.8).

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

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

Venetoclax film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole with a meal and water at approximately the same time each day. 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.

Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration

phase (see sections 4.2 and 4.5).

Use of preparations containing St. John's wort is contraindicated in patients treated with venetoclax (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Tumour lysis syndrome

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

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

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

Concomitant use of venetoclax 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).

Concomitant use of venetoclax with P-gp and BCRP inhibitors at initiation and during the dose titration-phase should be avoided. Alternative treatments should be considered. If a P-gp and BCRP inhibitor must be used patients should be monitored more closely for signs of toxicities (see section 4.5).

Neutropenia

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

Immunisation

The safety and efficacy of immunisation with live attenuated vaccines during or following venetoclax therapy have not been studied. Live vaccines should not be administered during treatment with venetoclax 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. If a CYP3A4 inducer must be used, closely monitor patients for lack of efficacy (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).

4.5 Interaction with other medicinal products and other forms of interaction

Venetoclax is predominantly metabolized by CYP3A.

Agents that may increase 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} by 2.3-fold and AUC_{∞} by 6.4-fold. Concomitant use of venetoclax with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole) at initiation and during the dose-titration phase is contraindicated due to increased risk for TLS (see section 4.3).

At initiation and during the dose-titration phase, concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation dose of venetoclax and the doses for the titration phase (see section 4.2) should be reduced by at least 2-fold. Patients should be monitored more closely for signs and symptoms of TLS.

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

For patients who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by at least 2-fold when used concomitantly with moderate CYP3A inhibitors and by at least 4-fold when used concomitantly with strong CYP3A inhibitors. 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). Patients should be monitored more closely for signs of toxicities.

OATP1B1/1B3 and P-gp inhibitors
Venetoclax is a substrate for P-gp and BCRP (see section 5.2). Co-administration of a 600 mg single dose of rifampin, an OATP1B1/1B3 and P-gp inhibitor, in 11 healthy subjects increased venetoclax C_{max} by 106% and AUC_{∞} by 78%. No dose adjustment is recommended in combination with OATP1B1/1B3 or P-gp inhibitors. Patients should be monitored closely for signs of toxicities.

Agents that may decrease venetoclax plasma concentrations

CYP3A inducers

Co-administration of 600 mg once daily rifampin, 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, rifampin) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced (see section 4.3).

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

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 and BCRP inhibitor and a weak OATP1B1 inhibitor in vitro. Co-administration of narrow therapeutic index P-gp or BCRP substrates (e.g., digoxin, dabigatran, everolimus, and sirolimus) with venetoclax should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax to minimise a potential interaction in the gastrointestinal tract. Monitoring of statin (an OATP1B1 substrate) toxicity is recommended when concomittantly used with venetoclax.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women should avoid becoming pregnant while taking venetoclax 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 children potential not using highly efective contraception.

Breast-feeding

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

A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with venetoclax.

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

Fatigue has 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

The safety of venetoclax is based on pooled data of 296 patients treated with venetoclax in two phase 2 studies and one phase 1 study. In all, the studies enrolled previously treated CLL patients, including 188 patients with 17p deletion and 94 patients who had failed a B-cell receptor pathway inhibitor. Patients were treated with venetoclax 400 mg monotherapy once daily following a dose-titration schedule.

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

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

Tabulated summary of adverse reactions

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

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

System organ class	Frequency (all grades)	Preferred term (N=296)

Infections and infestations	Very common	Upper respiratory tract infection
	Common	Pneumonia Urinary tract infection
Blood and lymphatic system disorders	Very common	Neutropenia
		Anaemia
	Common	Febrile neutropenia
		Lymphopenia
Metabolism and nutrition disorders	Very common	Hyperphosphataemia
	Common	Tumour lysis syndrome Hyperkalaemia Hyperuricaemia Hypocalcaemia
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Nausea Constipation
General disorders and administration site conditions	Very common	Fatigue
Investigations	Common	Blood creatinine increased

Discontinuation and dose reductions due to ADRs
Discontinuations due to adverse reactions occurred in 9.1% of patients.
Dosage adjustments due to adverse reactions occurred in 11.8% of patients.

Description of selected adverse reactions

Tumour lysis syndrome
Tumour lysis syndrome is an important identified risk when initiating venetoclax. 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 (see section 4.2). 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.

In 122 CLL patients starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 3%. All events were laboratory TLS (laboratory abnormalities that met ≥2 of the following criteria within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L; or were reported as TLS events)

and occurred in patients who had a lymph node(s) ≥5 cm or ALC ≥25 x 10^9/L. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥50 mL/min.

4.9 Overdose

There is no specific antidote for venetoclax. Patients who experience overdose should be closely monitored and appropriate supportive treatment provided; during dose-titration phase. Venetoclax 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: other antineoplastic agents, ATC code: not yet assigned

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 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 nonclinical 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

Patients with CLL harbouring 17p deletion or TP53 mutations

The safety and efficacy of venetoclax in 107 patients with previously treated CLL with 17p deletion were evaluated in a single arm, open-label, multi-center study (M13-982). Patients followed a 4- to 5-week dose-titration schedule starting at 20 mg and increasing to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive venetoclax 400 mg once daily until disease progression or unacceptable toxicity was observed. The median age was 67 years (range: 37 to 85

years); 65.4% were male, and 97.2% were white. The median time since diagnosis was 6.8 years (range: 0.1 to 32.1 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, 38.3% with prior rituximab, and 93.5% with a prior alkylator (including 32.7% with prior bendamustine). At baseline, 53.3% of patients had one or more nodes ≥5 cm, and 50.5% had ALC ≥25 x 109/L. Of the patients, 37.4% (34/91) were fludarabine refractory, 81.1% (30/37) harboured the unmutated IgVH gene, and 72.3% (60/83) had TP53 mutation. The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Efficacy results are shown in Table 4.

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

	IRC assessment (N=107)[a]	Investigator assessment (N=107)[a]
ORR, % (95% CI)	79.4 (70.5, 86.6)	73.8 (64.4, 81.9)
CR + CRi, %	7.5	15.9
nPR, %	2.8	3.7
PR, %	69.2	54.2
DOR, % (95% CI) 12-month estimate	84.7 (74.5, 91.0)	89.1 (79.2, 94.4)

[a]One patient did not harbour the 17p deletion.
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, IRC = independent review committee; nPR = nodular PR; PR = partial remission.

The median time to first response was 0.8 months (range: 0.1 to 8.1 months). Median duration of response (DOR) or median progression-free survival (PFS) has not been reached with approximately 12 months median follow-up.

Minimal residual disease (MRD) was evaluated using flow cytometry in 45 of 107 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (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). Seventeen percent (18/107) of patients were MRD negative in the peripheral blood, including 6 patients who were also MRD negative in the bone marrow.

There were 73 patients who completed the Global Health Status/Quality of Life (GHS/QoL) assessment, and 76 patients who completed both the Emotional (EF) and Social Functioning (SF) assessments in the EORTC QLQ-C30 questionnaire at both baseline and week 24. There were 74 and 77 patients, respectively, who completed the Role Functioning (RF) and the Fatigue symptom scale assessments at both baseline and week 24. Clinically relevant improvement was a change from baseline to 10 points, which was considered the minimum important difference (MID). Following treatment with venetoclax, the percentage of patients with a 10-point improvement from baseline to week 24 for each domain was: 41.1% for GHS/QoL, 36.8% for EF, 44.7% for SF, 51.4% for RF, and

24.7% for Fatigue.

Patients with CLL who have failed a B-cell receptor pathway inhibitor

The efficacy and safety of venetoclax in patients with CLL who had been previously treated with and failed ibrutinib or idelalisib therapy was evaluated in an open-label, multi-center, non-randomised, phase 2 study (M14-032). Patients received venetoclax via a recommended dose-titration schedule starting at 20 mg once daily for 7 days and increasing weekly to 50 mg, 100 mg, 200 mg and finally 400 mg once daily over 5 weeks. Patients continued to receive venetoclax 400 mg once daily until disease progression or unacceptable toxicity was observed.

At the time of data cutoff, 64 patients were enrolled and treated with venetoclax. Of these, 43 patients had received prior ibrutinib therapy (Arm A) and 21 had received prior idelalisib therapy (Arm B). The median age was 67 years (range: 48 to 85 years), 75% were male, and 92.2% were white. The median time since diagnosis was 8.7 years (range: 0.3 to 18.5 years; N=48). Chromosomal aberrations were 11q deletion (29.7%, 19/62), 17p deletion (35.9%, 23/61), *TP53* mutation (26.2%, 16/61) and unmutated IgVH (85.7%, 36/42). At baseline, 40.6% of patients had one or more nodes ≥5 cm and 37.5% had ALC ≥25 x 10^9/L. The median number of prior oncology treatments was 4 (range: 1 to 12 treatments) in ibrutinib-treated patients and 3 (range: 1 to 11) in idelalisib-treated patients. Overall, 69% of patients received prior nucleoside analogue, 88% rituximab, 31% other monoclonal antibodies, and 86% alkylating agent (including 42% with bendamustine). At the time of evaluation, median duration of treatment with venetoclax was 8.2 months (range: 0.1 to 13.9 months). Of the 43 ibrutinib-treated patients, 60.4% had discontinued ibrutinib treatment due to progressive disease. Of the 21 idelalisib-treated patients, 28.6% had discontinued idelalisib treatment due to progressive disease.

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

Table 5: Overall response rate (ORR) and duration of response (DOR) as assessed by investigator in patients who have failed a B-cell receptor pathway inhibitor (Study M14-032)

	Arm A (ibrutinib failures) (N=43)	Arm B (idelalisib failures) (N=21)[a]	Total (N=64)
ORR, % (95% CI)	60.5 (44.4, 75.0)	33.3 (14.6, 57)	51.6 (38.7, 64.2)
CR + CRi, %	4.7	9.5	6.3
nPR, %	4.7	0	3.1
PR, %	51.2	23.8	42.2
DOR, % (95% CI) 12-month estimate	90.9 (68.1, 97.6)	NA	92.3 (72.5, 98.0)

[a]Six patients did not have a 24-week assessment at the time of data cutoff.
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, NA = not applicable, nPR = nodular PR; PR = partial remission.

The efficacy data were further evaluated by an IRC demonstrating a combined ORR of 62.5% (arm A: 69.8%; arm B: 47.6%). One patient (ibrutinib failure) achieved complete remission with incomplete marrow recovery.

Table 6. Investigator–assessed efficacy results for subgroups according to 17p deletion or TP53 mutation status in study M14-032

	Arm A (ibrutinib failures)		Arm B (idelalisib failures)	
	17p deletion N=21	*TP53* mutation N=15	17p deletion N=2	*TP53* mutation N=1
ORR, % (95% CI)	61.9 (38.4, 81.9)	53.3 (26.6, 78.7)	100 (15.8, 100)	100 (2.5, 100)
CR + CRi, %	4.8	6.7	50	100
nPR, %	0	0	0	0
PR, %	57.1	46.7	50	0
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, NA = not applicable, nPR = nodular PR; PR = partial remission.				

Following treatment with venetoclax, median time to first response was 1.6 months (range: 1.6 to 5.6 months) for patients who were previously treated with ibrutinib and 1.6 months (range: 1.6 to 3.5 months) for patients previously treated with idelalisib. Median PFS and DOR were not reached.

Twenty percent (13/64) of patients were MRD negative in the peripheral blood.

Elderly patients

Of the total number of patients in M13-982 study, 57% were 65 years or older. There were no overall differences in safety or efficacy observed in comparison with younger patients.

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

Following multiple oral administrations, maximum plasma concentration of 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 µg/mL and AUC_{24} was 32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose.

Effect of food

Administration with a low-fat meal increased 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 µM (0.87-26 µg/mL). The mean blood-to-plasma ratio was 0.57. The population estimate for apparent volume of distribution (Vd_{ss}/F) of venetoclax ranged from 256-321 L in patients.

Metabolism

In vitro studies demonstrated that venetoclax is predominantly metabolized 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 due to high plasma protein binding. 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 219 subjects with mild renal impairment (CrCl ≥60 and <90 mL/min), 86 subjects with moderate renal impairment (CrCl ≥30 and <60 mL/min) and 217 subjects with normal renal function (CrCl ≥90 mL/min), venetoclax exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with severe renal impairment (CrCl <30 mL/min) or patients on dialysis (see section 4.2).

Hepatic impairment
Based on a population pharmacokinetic analysis that included 74 subjects with mild hepatic

impairment, 7 subjects with moderate hepatic impairment and 442 subjects with normal hepatic function, 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. The pharmacokinetics of venetoclax has not been studied in subjects with severe hepatic impairment (see section 4.2).

Effects of age, sex, and weight

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

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/gentotoxicity
Carcinogenicity studies have not been conducted with venetoclax.

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 the recommended dose. 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 the recommended dose. In rabbits, venetoclax produced maternal toxicity, but no foetal toxicity at exposures of 0.1 times the human exposure at the recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Venetoclax 10 mg film-coated tablets
Tablet Core
Copovidone
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 (E1521)
Talc (E553b)

Venetoclax 50 mg film-coated tablets
Tablet Core
Copovidone
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 (E1521)
Talc (E553b)

Venetoclax 100 mg film-coated tablets:
Tablet Core
Copovidone
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 (E1521)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Venetoclax tablets are supplied in daily dose PVC/PE/PCTFE aluminium foil blisters or in a bottle in induction sealed high density polyethylene (HDPE) bottles with child resistant polypropylene caps.

10 mg tablets: 14 tablets
50 mg tablets: 7 tablets
100 mg tablets: 7 or 14 tablets; bottle containing 120 tablets

6.6 Special precautions for disposal and other handling

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

7. SCIENTIFIC OPINION HOLDER

AbbVie Ltd
Maidenhead
SL6 4UB
United Kingdom

8. EAMS NUMBER

41042/0001

9. DATE OF SCIENTIFIC OPINION

Additional information:

Each prescribing oncologist will have to complete a **Treatment Access Request Form** to ensure eligibility within the scheme and to collect anonymised patient data.

An **Informed Consent Form** will be provided to be completed with the patient.

AbbVie will arrange delivery of the following:

EAMS Treatment Protocol
This includes the following materials:

- Summary of Product Characteristics;
- Patient Information leaflet;
- Adverse Event Report Form;
- Pregnancy Notification Form;
- Treatment Access Re-supply Form.

Training
The training will ensure understanding of:

- the dose ramp up stage, including the management of the Tumour Lysis Syndrome risk;
- adverse event reporting.

The prescribing oncologist will be required to complete the **Treatment Access Re-Supply Form** on which there will be confirmation that all adverse events have been reported. The order should be placed two weeks before the next planned cycle is due.

The prescribing oncologist is requested to inform AbbVie if a patient discontinues treatment by emailing global@idispharma.com with the last date of treatment.

Contact information:

To initiate the registration process for EAMS e-mail **IDIS Customer Services:** global@idispharma.com

For medical information enquiries e-mail **AbbVie Medical Information:** ukmedinfo@abbvie.com or telephone: 01628 561092 (option 3)