Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Venetoclax

Proprietary Product Name: Venclexta

Sponsor: AbbVie Pty Ltd

September 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AML	Acute myeloid leukaemia
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific Annex
BCL-2	B-cell lymphoma 2
BIM	B-cell lymphoma 2 interacting mediator of cell death
BSC	Best supportive care
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CMI	Consumer Medicines Information
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete blood count recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
DLP	Data lock point
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration (United States)
HMA	Hypomethylating agent
IWG	International Working Group
LDAC	Low-dose cytarabine
MLFS	Morphologically leukaemia-free status
NCCN	National Comprehensive Cancer Network (United States)

Abbreviation	Meaning
NCI	National Cancer Institute (United States)
ORR	Overall response rate
OS	Overall survival
PD	Disease progression
PI	Product Information
PK	Pharmacokinetic(s)
PR	Partial remission
PSUR	Periodic safety update report
QD	Once daily (*Latin: quaque die)*
RBC	Red blood cell
RD	Resistant disease
RMP	Risk management plan
SAE	Serious adverse event
TEAE	Treatment emergent adverse event
TLS	Tumour lysis syndrome
US	United States (of America)
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Product name:	Venclexta
Active ingredient:	Venetoclax
Decision:	Approved for provisional registration;[1]
Date of decision:	28 January 2020 (submission PM-2018-05208-1-6) 5 February 2020 (submission PM-2019-04393-1-6)
Date of entry onto ARTG:	11 February 2020 (submission PM-2018-05208-1-6) 14 February 2020 (submission PM-2019-04393-1-6)
ARTG numbers:	267441, 267442, 267443, 267444, 267445
, *Black Triangle Scheme:*[2]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	AbbVie Pty Ltd Level 7, 241 O'Riordan Street, Mascot, NSW 2020
Dose form:	Film coated tablet
Strengths:	10 mg, 50 mg and 100 mg
Containers:	Wallet (with blister pack), blister pack and bottle
Pack sizes:	10 mg wallet: 14 tablets 50 mg wallet: 7 tablets 100 mg bottle: 120 tablets, 180 tablets

[1] As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.
The provisional registration period is 2 years starting on the day registration commences. Up to two extensions of up to 2 years can be applied for, resulting in a possible maximum provisional registration period of 6 years. The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available.
[2] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

100 mg blister pack: 7 tablets, 14 tablets and 112 tablets

Starting pack for CLL: 42 tablets (14 x 10 mg, 7 x 50 mg, 7 x 100 mg, 14 x 100 mg)

Approved therapeutic use: *Acute Myeloid Leukaemia*

Venclexta, as part of combination therapy, is indicated for the treatment of newly diagnosed adult patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.

This medicine has provisional approval in Australia for the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy. The decision to approve this indication has been made on the basis of interim data (overall response rate and duration of response). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

Route of administration: Oral

Dosage: ***Acute myeloid leukaemia***

The dose of Venclexta depends upon the combination agent. Initiate azacitidine or low dose cytarabine on Day 1. The Venclexta dosing schedule (including ramp-up) is shown below.

- Day 1: 100 mg
- Day 2: 200 mg
- Day 3: 400 mg
- Day 4 and beyond:
    - 400 mg when dosing in combination with azacitidine
    - 600 mg when dosing in combination with low dose cytarabine

Venclexta, in combination with azacitidine or low dose cytarabine, should be continued until disease progression or unacceptable toxicity is observed.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by AbbVie Pty Ltd (the sponsor) to provisionally register Venclexta (venetoclax) 10 mg, 50 mg and 100 mg film coated tablet for the following indication proposed extension of indications:

> *Venclexta is indicated for the treatment of newly diagnosed patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.*

Acute myeloid leukaemia (AML) is an aggressive malignancy characterised by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood, and occasionally extramedullary tissues, which disrupts normal haematopoiesis.[3,4] AML is a heterogeneous disease, encompassing a large number of distinctly different subtypes that may have different clinical presentations and differing responses to treatment.[5,6]

In Australia, the median age at diagnosis of AML is 69 years, according to 2013 incidence data.[7] AML in the elderly patient population is a biologically and clinically distinct disease with a diminished response to chemotherapy, low remission rates, short disease-free survival and short overall survival (OS). Due to improvements in supportive care and the introduction of less intensive chemotherapy regimens the 1 year survival rate has improved slightly over the last 30 years for patients between the ages of 65 and 74, but it has not changed for patients 75 years of age and older.[8,9]

No single standard of care exists for older patients with AML. Both the National Comprehensive Cancer Network (NCCN);[10] and the European LeukaemiaNet (ELN);[11] recommendations for induction treatment for patients aged ≥ 60 years take into account not only the patient's chronologic age, but additional factors that impact on a patient's ability to tolerate intensive chemotherapy, including performance status, high-risk factors, and any co-morbidities.[12]

Treatment options for induction therapy vary in intensity and include the standard 3 + 7 regimen consisting of 3 days of an anthracycline (for example, daunorubicin, idarubicin, or mitoxantrone) combined with 7 days of cytarabine, low dose cytarabine (LDAC),

[3] Showel MM and Levis M. (2014). Advances in treating acute myeloid leukemia. *F1000Prime Rep*, 6:96. doi:10.12703/P6-96
[4] Deschler B., Lübbert M. (2008). Acute Myeloid Leukemia: Epidemiology and Etiology. In: Acute Leukemias. Hematologic Malignancies. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-72304-2_3
[5] Vardiman JW et al. (2009). The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood, 114 (5): 937–951. doi: 10.1182/blood-2009-03-209262
[6] Bryan JC, Jabbour EJ. (2015). Management of Relapsed/Refractory Acute Myeloid Leukemia in the Elderly: Current Strategies and Developments. *Drugs Aging.* 32(8):623-637. doi:10.1007/s40266-015-0285-6
[7] Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW.
[8] Thein MS et al. (2013). Outcome of older patients with acute myeloid leukemia: an analysis of SEER data over 3 decades. *Cancer*, 119(15):2720-2727. doi:10.1002/cncr.28129
[9] Nazha A, Ravandi F. (2014). Acute myeloid leukemia in the elderly: do we know who should be treated and how? *Leuk Lymphoma*, 55(5):979-987. doi:10.3109/10428194.2013.828348
[10] The **National Comprehensive Cancer Network (NCCN)** is an alliance of 30 cancer centres in the United States, most of which are designated by the National Cancer Institute (one of the US National Institutes of Health) as comprehensive cancer centres. It is a non-profit organisation with offices in Plymouth Meeting, Pennsylvania, USA.
[11] The objective of the **European LeukemiaNet (ELN)** is to integrate the leading leukaemia trial groups (chronic myeloid leukaemia (CML), acute myeloid leukaemia (AML), acute lymphoid anaemia (ALL), chronic lymphoid leukaemia (CLL), myelodysplastic syndrome (MDS), and chronic myeloproliferative disorders (CMPD)), their interdisciplinary partners (diagnostics, treatment research, registry, guidelines), industry and subject matter experts across Europe to form a cooperative network for advancements in leukaemia-related research and health care and cure.
[12] Al-Ali HK. (2014). The role of hypomethylating agents in the treatment of elderly patients with AML. *J Geriatr Oncol,* 5(1):89-105

clofarabine, or hypomethylating agents (HMA) (for example, azacitidine, and decitabine); alternatively, patients may be encouraged to participate in a clinical trial.[6,13]

Although standard induction therapy has a 45% to 55% response rate in patients aged ≥ 60 years, older patients experience poor long-term survival due to a high risk of relapse and treatment-related mortality.[13] Induction therapy related mortality for patients 55 years of age or older has been estimated at 15% to 20%.[14] As a result, low-intensity treatment options are currently recommended by NCCN guidelines for the treatment of AML in patients aged ≥ 60 years and include HMA agents (such as azacitidine or decitabine) and LDAC. In contrast, the ELN guidelines recommend standard induction therapy for patients aged 60 to 74 years with the Eastern Cooperative Oncology Group (ECOG) performance status < 2;[15] and no co-morbidities, and LDAC for patients aged ≥ 75 years or ≥ 65 years with a performance status of ≥ 2, co-morbidities, or organ dysfunction.[14] The European Society for Medical Oncology (ESMO);[16] guidelines recommend that elderly patients and those with significant co-morbidities receive best supportive care (BSC) or palliative systemic treatment such as LDAC or a HMA.[13] Notably, ESMO and NCCN guidelines are endorsed by the National Cancer Expert Reference Group, Cancer Australia and Cancer Council Australia.[17,18,19]

In Australia, in addition to BSC, two treatment pathways are available for patients ineligible for intensive chemotherapy, namely azacitidine and LDAC. Azacitidine is registered for the treatment of patients with AML with 20 to 30% blasts and multi-lineage dysplasia (according to World Health Organization (WHO) Classification), in whom allogeneic stem cell transplantation is not indicated.[20] Cytarabine is also registered for the treatment of AML, either as monotherapy or in combination with other antineoplastic agents, and is administered in low doses.[21]

Venetoclax is a small molecule inhibitor of B-cell lymphoma 2 (BCL-2), a molecule which suppresses apoptosis in haematologic cells. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like B-cell lymphoma interacting mediator of cell death (BIM), triggering mitochondrial outer membrane permeabilisation, the release of cytochrome *c* from mitochondria and the activation of caspases.

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[13] Erba HP. (2015). Finding the optimal combination therapy for the treatment of newly diagnosed AML in older patients unfit for intensive therapy. *Leuk Res*, 39(2):183-91

[14] Cruijsen M et al. (2015). Clinical results of hypomethylating agents in AML treatment. J Clin Med;4:1-17.

[15] **ECOG Performance Status:** The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

[16] The **European Society for Medical Oncology (ESMO)** is Europe's leading professional organisation for medical oncology. With more than 25,000 members representing oncology professionals from over 160 countries worldwide, ESMO creates a society of reference for oncology education and information.

[17] Fey MF, Buske C. (2013). ESMO Guidelines Working Group. Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. *Ann Oncol,* 24 (Suppl 6):vi138-43.

[18] O'Donnell MR, et al. (2017). Acute myeloid leukemia, version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr CancNetw*, 15:926–57.

[19] Cancer Australia. Clinical practice guidelines for Leukaemia for Health Professionals. Available from: https://leukaemia.canceraustralia.gov.au/health-professionals. Last accessed 6 January 2020.

[20] Vidaza Product Information. Version 1.12, dated 17 January 2018. Sponsored by Celgene Pty Limited.

[21] Cytarabine Product Information, dated 1 November 2017. Sponsored by Pfizer Australia Pty Limited.

The current submissions seek to extend the indications to include AML in combination therapy with low dose cytarabine (submission PM-2018-05208-1-6) and in combination therapy with azacitidine (submission PM-2019-04393-1-6) through the provisional approval pathway.

Regulatory status

Venclexta received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 5 January 2017 for the following indication:

> *Venclexta is indicated for the treatment of:*
>
> - *patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) with 17p deletion, or*
> - *patients with relapsed or refractory CLL for whom there are no other suitable treatment options.*
>
> *Note to indications. The indications are approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life have not been established.*

The TGA approved an extension of indication for Venclexta on 8 October 2018, for the following indication:

> *Venclexta in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.*

At the time the TGA considered this application, a similar application had been granted accelerated approval;[22] for the treatment of AML by the United States (US) Food and Drug Administration (FDA) (approved on 21 November 2018). The current indications in the US are:

> *Venclexta is a BCL-2 inhibitor indicated:*
>
> - *For the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).*
> - *In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[22] The FDA's **accelerated approval** approach allows drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint or an intermediate clinical endpoint. In the accelerated approval process, a surrogate endpoint is a marker, for example a laboratory measurement, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug. Additional data from confirmatory trials is then required to verify the clinical benefit.

II. Registration timeline

The following tables captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-05208-1-6

Description	Date
Designation (Orphan;[23] and Provisional)	29 October 2018
Submission dossier accepted and first round evaluation commenced	31 January 2019
First round evaluation completed	1 July 2019
Sponsor provides responses on questions raised in first round evaluation	30 July 2019
Second round evaluation completed	11 September 2019
Delegate's Overall benefit-risk assessment	6 January 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	28 January 2020
Completion of administrative activities and registration on the ARTG	11 February 2020
Number of working days from submission dossier acceptance to registration decision*	227

*Statutory timeframe for standard applications is 255 working days

Table 2: Timeline for Submission PM-2019-04393-1-6

Description	Date
Designation: Provisional Orphan	 17 September 2019 25 September 2019
Submission dossier accepted and first round evaluation commenced	31 October 2019

[23] 'Orphan drugs' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related **orphan designation** is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

Description	Date
First round evaluation completed	7 November 2019
Sponsor provides responses on questions raised in first round evaluation	26 November 2019
Second round evaluation completed	4 December 2019
Delegate's Overall benefit-risk assessment	6 January 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	5 February 2020
Completion of administrative activities and registration on the ARTG	14 February 2020
Number of working days from submission dossier acceptance to registration decision*	67

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The following points were summarised in the nonclinical evaluation:

- Published data showing killing of human AML cells by venetoclax *in vitro* and *in vivo* in mice, and recognition of the involvement of BCL-2 in AML cell survival, offer support for utility for venetoclax in the proposed new indication.
- Increased exposure and increased toxicity follow the increase in maximum recommended human dose (from 400 mg/day to 600 mg/day) associated with the newly proposed indication. The dosing instructions for AML direct treatment to be continued until disease progression or unacceptable toxicity is observed.
- The major human metabolite, M27, is not seen to contribute (or at least significantly so) to toxicity in venetoclax-treated patients, based on the findings of a newly evaluated study in mice.
- There are no nonclinical objections to the proposed extension of indications for Venclexta.

- The proposed PI document should be revised as directed.

The submission did not include new toxicology data although the pre-clinical evaluator has noted the increased drug exposure involved in the increase from 400 mg to 600 mg daily dosing. However, the nonclinical evaluator has noted that the originally submitted nonclinical program remains sufficient to cover the increased dose. In general, the nonclinical evaluator has raised no objections to registration of the new indication and dosage.

Clinical

The submitted dossier include three studies; Studies M14-387, M14-212 and M14-358, of which Study M14-387 and Study M14-358 were considered pivotal by the clinical evaluator. A composite pharmacokinetic report was produced (R&D/18/0339) based on data from the three clinical studies.

There was no paediatric data in this submission.

Pharmacology

Pharmacokinetic (PK) analysis indirectly examined the effect of venetoclax administration with cytarabine, azacitidine and decitabine using a population kinetics model and data from 400 mg, 600 mg, 800 mg and 1200 mg doses administered in trials.

Efficacy

Venetoclax with cytarabine

The pivotal efficacy analysis of this combination was provided by Study M14-387.[24] This trial was a Phase I/II study of treatment naïve patients with AML who were 60 years old or older and ineligible for standard cytarabine and anthracycline based induction therapy. All patients (n = 82) received venetoclax + LDAC. Treatment was continued until disease progression, withdrawal or toxicity necessitated an interruption. The primary endpoint of the trial was overall response rate (ORR).

The combination of venetoclax + LDAC achieved a response rate of 54.9% (95% confidence interval (CI), 43.5 to 65.9%) (see Table 3).

Table 3: Study M14-387 Overall response rate for venetoclax 600 mg once daily + low dose cytarabine therapy

Outcome measure – best IWG response	Venetoclax 600 mg QD + LDAC (n = 82)
Objective response rate (CR + CRi + PR), n (%) [95% CI]	45 (54.9%) [43.5, 65.9]
Leukemia response rate (CR + CRi + PR + MLFS), n (%) [95% CI]	51 (62.2%) [50.8%, 72.7%]
Complete remission (CR), n (%) [95% CI]	21 (25.6%) [16.6, 36,4]
Complete remission with incomplete blood count recovery (CRi), n (%) [95% CI]	23 (28.0%) [18.7, 39.1]

[24] Study M14-387; title: 'A Study Evaluating Venetoclax in Combination With Low-Dose Cytarabine in Treatment-Naïve Participants With Acute Myelogenous Leukemia.' ClinicalTrials.gov Identifier: NCT02287233; EudraCT Number: 2014-002610-23.

Outcome measure – best IWG response	Venetoclax 600 mg QD + LDAC (n = 82)
Partial remission (PR) n (%)	1 (1.2%)
Morphologically leukaemia free state (MLFS) n (%)	6 (7.3%)
Resistant disease (RD) n (%)	19 (23.2%)
Disease progression (PD) n (%)	4 (4.9%)
Discontinued with no response data (DS) n (%)	8 (9.8%)
Non-response but still active (NR) n (%)	0
Study duration (months), median [range] n (%)	20.0 [6.0 to 34.3]
Study survival follow-up (months), median [range] n (%)	7.1 [0.3 to 34.3]

IWG = International Working Group; QD = once daily; LDAC = low dose cytarabine; CR = complete remission; CRi = complete remission with incomplete blood count recovery; PR = partial remission; CI = confidence interval; MLFS = morphologically leukemia-free status; RD = resistant disease; PD = disease progression; DS = discontinued with no response; NR = non-response but still active.

The median OS was 10.1 months (95% CI, 5.7 to 14.2 months) (see Table 4). The results of therapy were more favourable in patients ≥ 75 years of age than in those < 75 years of age. The sponsor noted that this may be due to co-morbidities which would render a younger person ineligible for intensive therapy, although the difference could be due to random variation.

Table 4: Study M14-387 Comparison of outcomes by age of patient

Outcome variables	Overall (n = 82)	≥ 75 years (n = 40)	< 75 years (n = 42)
Rate, n (%) [95% CI]			
CR	21 (25.6%) [16.6, 36.4]	11 (27.5%) [14.6, 23.9]	10 (23.8%) [12.1, 39.5]
CR + CRh	38 (46.3%) [35.3, 57.7]	22 (55.0%) [38.5, 70.7]	16 (38.1%) [23.6, 54.4]
CR + CRi	44 (53.7%) [42.3, 64.7]	24 (60.0%) [43.3, 75.1]	20 (47.6%) [32.0, 63.6]
RBC transfusion independence	39 (47.6%) [36.4, 58.9]	23 (57.5%) [40.9, 73.0]	16 (38.1%) [23.6, 54.4]
Platelet transfusion independence	49 (59.8%) [48.3, 70.4]	26 (65.0%) [48.3, 79.4]	23 (54.8%) [38.7, 70.2]
Median duration, months [95% CI]			
Median duration of CR	14.8 [5.6, -]	14.8 [2.7, -]	11.6 [1.8, -]

Outcome variables	Overall (n = 82)	≥ 75 years (n = 40)	< 75 years (n = 42)
Median duration of CR + CRh	11.0 [6.1, -]	14.3 [5.6, -]	8.3 [4.1, -]
Median duration of CR + CRi	8.1 [5.3, 14.9]	14.1 [5.3, -]	6.1 [2.6, -]
Median overall survival	10.1 [5.7, 14.2]	14.9 [6.1, -]	6.5 [3.7, 11.7]

QD = once daily; LDAC = low dose cytarabine; CR = complete remission; CRi = complete remission with incomplete blood count recovery; CI = confidence interval; CRh = complete remission with partial hematologic recovery; RBC = red blood cell.

Venetoclax with azacitidine

The pivotal analysis supporting the combination of venetoclax and azacitidine was provided by Study M14-358.[25] This was a Phase Ib study in 212 patients with treatment naïve patients with AML who were ineligible for intensive therapy due to age and/or comorbidities. Patients received venetoclax daily, and azacitidine (75 mg/m^2) or decitabine (20 mg/m^2) on days 1 to 7 or days 1 to 5 of each 28 day cycle respectively. The primary endpoint of the study was the complete remission (CR) rate.

For the 127 subjects receiving any dose of venetoclax in combination with azacitidine, the CR rate was 38.6% (49 subjects), and the complete remission with incomplete blood count recovery (CRi) rate was 26.0% (33 subjects) (see Table 5). The combined CR+CRi rate was 64.6% (n = 82, 95% CI 55.6 to 72.8%). The partial remission (PR) rate was 0.8% (one subject), making the ORR 65.4% (83 subjects).

Median OS for 400 mg venetoclax plus azacitidine (n = 84) is 14.9 months (10.2,-).

Table 5: Study M14-358 Results for venetoclax combination therapy

	All Doses Of Venetoclax + Azacitidine (N = 127)	All Doses Of Venetoclax + Decitabine (N = 73)
Subject best IWG response – n (%)		
Complete remission (CR)	49 (38.6%)	37 (50.7%)
Complete remission with incomplete blood count recovery (CRi)	33 (26.0%)	16 (21.9%)
Partial remission (PR)	1 (0.8%)	1 (1.4%)
Morphologically leukemia-free state (MLFS)	18 (14.2%)	7 (9.6%)
Resistant disease (RD)	20 (15.7%)	6 (8.2%)
Disease progression (PD)	2 (1.6%)	0
Discontinued with no response data (DS)	4 (3.1%)	6 (8.2%)
Non-response but still active (NR)	0	0
Objective response rate (CR + CRi + PR) n (%) [95% CI]#	83 (65.4%) [56.4%, 73.6%]	54 (74.0%) [62.4%, 83.5%]
Leukemia response rate (CR + CRi + PR + MLFS) n (%) [95% CI]#	101 (79.5%) [71.5%, 86.2%]	61 (83.6%) [73.0%, 91.2%]
Duration of study (month) median [range]	16.4 [6.0 – 36.5]	21.1 [18.3 – 37.2]
Survival follow up (month) median [range]	8.6 [0.40 – 35.5]	16.2 [0.2 – 36.7]

95% confidence interval is from the exact binomial distribution.
Study duration is defined as cutoff date - first dose of study drug + 1.
Study survival follow up is defined as time from first dose of study drug to date of death, last known alive date, or cutoff date whichever is earlier.
Note: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; DS = discontinued with no response data; IWG = International Working Group; MLFS = morphologic leukemia-free state; NR = non-response but still active; PD = disease progression. Data included are subject to a cutoff date of 22 Dec 2017.

[25] Study M14-358; title: 'Study of ABT-199 (GDC-0199) in Combination With Azacitidine or Decitabine (Chemo Combo) in Subjects With Acute Myelogenous Leukemia (AML)'. ClinicalTrials.gov Identifier: NCT02203773; EudraCT Number: 2014-000687-18.

Safety

Venetoclax with cytarabine

In Study M14-387;[24] the median duration of exposure was 4.2 months. Of the 82 enrolled patients, 36 were exposed to venetoclax for > 24 weeks, 19 were exposed for > 52 weeks.

All patients suffered at least one treatment emergent adverse event (TEAE), and the majority of these were graded as 3 to 4 in intensity (see Table 6 and Table 7).

At the time of reporting, 68.3% of the patients enrolled in Study M14-387 had died. TEAE leading to death were reported in 22% of subjects (n = 18) (see Table 6). These included malignant neoplasm progression (6.1%), lung infection (2.4%), sepsis (2.4%) and intracranial haemorrhage (2.4%). Death from unknown cause, sudden death, hepatic failure, pneumonia, pulmonary sepsis, respiratory failure and embolism were reported in one subject each.

TEAE leading to discontinuation of therapy were reported in 32.9% of patients, and TEAEs leading to dose interruption were reported in 54.9% of patients (see Table 6).

Table 6: Study M14-387 Incidence of adverse events

Safety profile; High Level AE category	Venetoclax 600 mg QD + LDAC (n = 82); n (%)
Any TEAE	82 (100)
Any AE with NCI-CTCAE Grade 3 or 4	79 (96.3)
Any AE with NCI-CTCAE Grade ≥ 3	79 (96.3)
Any AE with a reasonable possibility of being related to venetoclax	73 (89.0)
Any AE with a reasonable possibility of being related to possibility LDAC	79 (96.3)
Serious AE	75 (91.5)
Any AE leading to hospitalisation	71 (86.6)
Any AE leading to venetoclax discontinuation	27 (32.9)
Any AE leading to LDAC discontinuation	30 (36.6)
Any AE leading to venetoclax interruption	45 (54.9)
Any AE leading to LDAC interruption	38 (46.3)
Any AE leading to venetoclax reduction	6 (7.3)
Any AE leading to LDAC reduction	1 (1.2)
Fatal AE (AE leading to death)	18 (22.0)
All deaths (treatment and non-treatment emergent)	56 (68.3)

QD = once daily; LDAC = low dose cytarabine; AE = adverse event; TEAE = treatment emergent adverse event; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 7: Study M14-387 Treatment emergent adverse events Grade 3 to 4 reported in ≥ 5% of subjects

TEAEs Grade 3 to 4 (Preferred Term)	Venetoclax 600 mg QD + LDAC (n = 82), n (%)
Any	79 (96.3)
Febrile neutropaenia	34 (41.5)
Thrombocytopaenia	31 (37.8)
White blood cell count decreased	28 (34.1)
Anaemia	22 (26.8)
Neutropaenia	22 (26.8)
Platelet count decreased	20 (24.4)
Lymphocyte count decreased	15 (18.3)
Neutrophil count decreased	14 (17.1)
Hypophosphataemia	13 (15.9)
Hypokalaemia	12 (14.6)
Sepsis	9 (11.0)
Pneumonia	9 (11.0)
Hypertension	9 (11.0)
Device related infection	7 (8.5)
Hyponatraemia	6 (7.3)
Fatigue	6 (7.3)
Hypotension	6 (7.3)
Decreased appetite	5 (6.1)

QD = once daily; LDAC = low dose cytarabine.

Tumour lysis syndrome (TLS) was reported in 2.4% (n = 2) of patients. These were laboratory-only events which occurred during the introduction of therapy. Neither of the patients with TLS developed clinical TLS and both recovered fully.

Thrombocytopaenia, diarrhoea and sepsis were reported more frequently in patients < 75 years of age than in those ≥ 75 years of age (see Table 8). Overall, the rates of TEAE were similar between the age groups. The rate of TEAE was also similar between male and female patients (data not shown).

Table 8: Study M14-387 Key treatment emergent adverse events in subjects ≥ 75 years of age and < 75 years of age

Key TEAEs	TEAE (any)		TEAE ≥ Grade 3		SAE	
	< 75 years n = 42; n (%)	≥ 75 years n = 40; n (%)	< 75 years n = 42; n (%)	≥ 75 years n = 40; n (%)	< 75 years n = 42; n (%)	≥ 75 years n = 40; n (%)
Any TEAE	42 (100)	40 (100)	41 (97.6)	38 (90.5)	38 (90.5)	37 (92.5)
Anaemia	10 (23.8)	12 (30.0)	10 (23.8)	12 (30.0)	0	1 (2.5)
Neutropaenia	9 (21.4)	13 (32.5)	9 (21.4)	13 (32.5)	0	1 (2.5)
Febrile neutropaenia	19 (45.2)	16 (40.0)	19 (45.2)	15 (37.5)	11 (26.2)	11 (28.2)
Thrombocytopaenia	18 (42.9)	13 (32.5)	18 (42.9)	13 (32.5)	1 (2.4)	0
Nausea	30 (71.4)	27 (67.5)	1 (2.4)	1 (2.5)	1 (2.4)	0
Vomiting	14 (33.3)	11 (27.5)	2 (4.8)	1 (2.5)	0	1 (2.5)
Diarrhoea	24 (57.1)	16 (40.0)	0	2 (5.0)	0	1 (2.5)
Constipation	14 (33.3)	15 (37.5)	0	0	1 (2.4)	0
Pneumonia	4 (9.5)	6 (15.0)	4 (9.5)	5 (12.5)	3 (7.1)	5 (12.5)
Sepsis	8 (19.0)	2 (5.0)	7 (16.7)	2 (5.0)	5 (11.9)	1 (2.5)

TEAE = treatment emergent adverse event; SAE = severe adverse event.

Venetoclax with azacitidine

The safety profile of venetoclax in Study M14-358;[25] was comparable with that in Study M14-387;[24] and between azacitidine and decitabine combination arms.

Post-marketing data was submitted with submission PM-2019-04393-1-6. In the latest periodic safety update report (PSUR), the cumulative exposure in clinical trials is estimated at 3996 patients, and the post market exposure is estimated to be 4299 patient treatment years in the reporting interval, and 10,820 patient treatment years since first approval. During the PSUR reporting period, the warnings and precautions section was updated to include serious infections, and sepsis was added to the adverse events (AE) table. These are well known risks of both AML, and venetoclax + azacitidine.

The clinical evaluator has noted that the US FDA has included a specific warning regarding increased mortality when venetoclax is used (off label) with bortezomib and dexamethasone in the treatment of multiple myeloma.

> 'Increased Mortality in Patients with Multiple Myeloma when Venclexta is added to Bortezomib and Dexamethasone. In a randomised trial (BELLINI;

NCT02755597);[26] in patients with relapsed or refractory multiple myeloma, the addition of Venclexta to bortezomib plus dexamethasone, a use for which Venclexta is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with Venclexta in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.'

The clinical evaluator has recommended that this warning be included in the Australian PI.

Risk management plan

- This evaluation considers the information related to the extension of indications to include AML in the risk management plan (RMP) documents (core RMP version 4.0 dated August 2018, with Australian specific Annex (ASA) version 3.0 dated November 2018) submitted through the current submission PM-2018-05208-1-6, and the 'summary of safety concerns' with pharmacovigilance and risk minimisation activities in the most recent RMP documents (core RMP version 5.0 dated March 2019; data lock point (DLP) 17 August 2018, with ASA version 3.1 dated March 2019). The sponsor has submitted the updated RMP documents (core RMP version 4.1 dated June 2019, and core RMP version 5.1 dated June 2019 with ASA version 3.2 dated July 2019) with the response to TGA's request for information.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in the table below.[27]

[26] Study M14-031; title: A Study Evaluating Venetoclax (ABT-199) in Multiple Myeloma Subjects Who Are Receiving Bortezomib and Dexamethasone as Standard Therapy. ClinicalTrials.gov Identifier: NCT02755597; EudraCT number: 2015-004411-20; also known as the BELLINI trial.

[27] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 9: Proposed summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Tumour lysis syndrome	ü[1]	ü[2]	ü[4]	–
	Neutropenia	ü	ü[2]	ü	–
	Serious infection	ü[1]	ü[2]	ü	–
Important potential risks	Embryo-foetal toxicity	ü[1]	–	ü	–
	Medication error	ü	–	ü[4, 5]	–
	Richter's transformation	ü	ü[2, 3]	–	–
	Second primary malignancy	ü	ü[2, 3]	–	–
	Toxicity in patients with severe hepatic impairment	ü	ü[3]	ü	–
Missing information	Safety in severe renal impairment	ü	–	ü	–
	Safety in long-term exposure (> 12 months)	ü	ü[3]	–	–

1: Specific adverse reaction follow-up questionnaire. 2: Observational cohort study. 3: Clinical trial. 4: Patient alert card in package. 5: Monthly starter pack includes a quick start guide with a dosing calendar, and weekly wallets.

The RMP evaluator has noted routine post-market activities which are acceptable.

Risk-benefit analysis

Delegate's considerations

These applications provide early evidence for the efficacy of venetoclax in the treatment of AML in patients for whom intensive therapy is not suitable. Given that the age of diagnosis for AML is frequently > 65 years, that this population has a high rate of comorbid conditions, and the acute prognosis of the malignancy, there is a need for better treatment options in this population.

The combination of venetoclax + LDAC and venetoclax + azacitidine produce clinically meaningful rates of complete response. However the Delegate notes that the addition of venetoclax confers an overall survival benefit of months compared to low dose chemotherapy, and that this would need to be balanced clinically against the significant toxicity which arises in combination therapy. The lack of a comparator arms in Studies M14-387 and M14-358 makes an assessment of the incremental increase in toxicity from adding venetoclax difficult, but the Delegate notes that most patients suffered at least one moderately severe TEAE.

The Delegate notes that the sponsor has applied for provisional registration and that this requires confirmatory evidence of efficacy and safety to be provided after registration.[1] These include updated study reports from Studies M14-387 and M14-358, as well as the Phase III Studies M16-043;[28] and M15-656.[29] These studies are expected to be available in the second quarter of 2020. They should allow for a more precise assessment of the risk-benefit of venetoclax component of combination therapy.

Proposed action

The Delegate intends to approve an additional indication for venetoclax and amend the wording of the existing indication to:

> *Acute Myeloid Leukaemia*
>
> *Venclexta, as part of combination therapy, is indicated for the treatment of newly diagnosed adult patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.*
>
> *This medicine has provisional approval in Australia for the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy. The decision to approve this indication has been made on the basis of interim data (overall response rate and duration of response). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*
>
> *Chronic Lymphocytic Leukaemia*
>
> *Venclexta in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.*
>
> *Venclexta monotherapy is indicated for the treatment of:*
>
> - *patients with relapsed or refractory CLL with 17p deletion, or*
> - *patients with relapsed or refractory CLL for whom there are no other suitable treatment options*.

The Delegate intends to include as conditions of the provisional registration of venetoclax that study reports for Studies M14-387;[24] M14-358;[25] M16-043;[28] and M15-656;[29] be submitted to the TGA for evaluation by 31 October 2021.

Advisory Committee considerations[30]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

[28] Study M16-043; title: 'A Study of Venetoclax in Combination With Low Dose Cytarabine Versus Low Dose Cytarabine Alone in Treatment Naive Patients With Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy'. ClinicalTrials.gov Identifier: NCT03069352; EudraCT number: 2016-003900-30.
[29] Study M15-656; title : 'A Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy.' ClinicalTrials.gov Identifier: NCT02993523; EudraCT number: 2016-001466-28.
[30] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the provisional registration of Venclexta (venetoclax) 10 mg, 50 mg and 100 mg film coated tablets, for the following extension of indications:

> *Acute Myeloid Leukaemia*
>
> *Venclexta, as part of combination therapy, is indicated for the treatment of newly diagnosed adult patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.*
>
> *This medicine has provisional approval in Australia for the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy. The decision to approve this indication has been made on the basis of interim data (overall response rate and duration of response). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

The provisional registration period for the above medicine(s) is two years starting on the day specified in the ARTG certificate of registration.

As such, the full indications at this time were:

> *Acute Myeloid Leukaemia*
>
> *Venclexta, as part of combination therapy, is indicated for the treatment of newly diagnosed adult patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.*
>
> *This medicine has provisional approval in Australia for the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy. The decision to approve this indication has been made on the basis of interim data (overall response rate and duration of response). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*
>
> *Chronic Lymphocytic Leukaemia*
>
> *Venclexta in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. Venclexta monotherapy is indicated for the treatment of:*
>
> - *patients with relapsed or refractory CLL with 17p deletion, or*
> - *patients with relapsed or refractory CLL for whom there are no other suitable treatment options.*

Specific conditions of registration applying to these goods

- Venclexta (venetoclax) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Venclexta must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Specifically the sponsor must conduct studies as described in the clinical study plan in version 3.2, dated July 2019 of the ASA. Interim and final clinical study reports (CSR) for the following studies should be submitted to TGA by 31 October 2021.

- Study M14-387
- Study M14-358
- Study M16-043
- Study M15-656

Further guidance for sponsors is available on the TGA website.

- The Venclexta core-RMP (version 4.1 dated June 2019; data lock point 29 May 2019), with ASA (version 3.2, dated July 2019), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs:

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs and should cover the entire period of provisional registration.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Venclexta approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at<https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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