Cancer Drugs Fund

Managed Access Agreement

Venetoclax for treating chronic lymphocytic leukaemia

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Venetoclax for treating chronic lymphocytic leukaemia [ID944]

Company name: AbbVie Ltd

Primary source of data collection: SACT

Date of Agreement	30/08/2017
NICE Agreement Manager	Linda Landells
NHS England Agreement Manager	Peter Clark
Public Health England Agreement Manager	Martine Bomb
AbbVie Agreement Manager	Carsten Edwards
[Other, e.g. research organisation] Agreement Manager	Not applicable

1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for venetoclax in chronic lymphocytic leukaemia (ID944). A positive recommendation within the context of a managed access agreement has been decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on upon publication of the managed access agreement. The data collection period is anticipated to conclude in December 2020; it is considered sufficient time to collect meaningful data (see section 7). The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

2.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the addendum to NICE's methods and processes when appraising cancer technologies.

3 Patient eligibility

3.1. Venetoclax monotherapy is indicated for the treatment of chronic lymphocytic leukaemia:

- in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.
- in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a BCRi.

3.2. Patient eligibility for treatment during the managed access arrangement period is as follows:

Venetoclax in treatment of chronic lymphocytic leukaemia in the absence of 17p deletion or TP53 mutation

- Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Confirmed diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma that requires treatment
- Patient has been tested for 17p deletion and TP53 mutation and both results are negative
- Patient must have progressive disease on or after chemoimmunotherapy
- Patient must also have progressive disease on or after treatment with a BCRi (e.g. ibrutinib, idelalisib)
- Patient has a performance status of 0-2
- Patients has been prospectively assessed for the risk of the development of tumour lysis syndrome following the start of venetoclax

- Patient has been assessed specifically for potential drug interactions with venetoclax
- Venetoclax is to be used as a single agent
- Venetoclax is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
- Venetoclax to be otherwise used as set out in its Summary of Product Characteristics

Venetoclax in treatment of chronic lymphocytic leukaemia in the presence of 17p deletion or TP53 mutation

- Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Confirmed diagnosis of chronic lymphocytic leukaemia or small lymphocytic lymphoma that requires treatment
- Patient is positive for testing for 17p deletion or TP53 mutation
- Patient must either have relapsed on or after a BCRi (eg ibrutinib, idelalisib) or there must be a contraindication to the patient receiving a BCRi
- Patient has a performance status of 0-2
- Patients has been prospectively assessed for the risk of the development of tumour lysis syndrome following the start of venetoclax
- Patient has been assessed specifically for potential drug interactions with venetoclax
- Venetoclax is to be used as a single agent
- Venetoclax is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)

- Venetoclax to be otherwise used as set out in its Summary of Product Characteristics

3.3. Patients presenting with 17p deletion/TP53 mutation who are unsuitable for a BCRi. These can be defined as follows in Table 1:

Table 1. Overview of characteristics including unsuitability for BCRi therapy

Ibrutinib	Idelalisib
History of atrial fibrillation/cardiac arrhythmias	Any autoimmune disease (e.g. connective tissue, Crohn's)
Required anticoagulants	Gastrointestinal dysfunction
Increased risk of bleeding from other causes (e.g. on aspirin/other antiplatelet agents)	Compromise of pulmonary function
Essential continuation of medications that cause drug-drug interactions	Prior opportunistic infection

'Adults patients unsuitable for a BCRi' is not further defined in the venetoclax SmPC as this is defined in the SmPC for the individual BCRi's, ibrutinib and idelalisib. Both ibrutinib and idelalisib have different mechanisms of action and distinct safety profiles that are reflected in 'Special warnings and precautions of use' and 'Interaction with other medicinal products'. Key safety concerns are bleeding risk and atrial fibrillation for ibrutinib and colitis, pneumonitis and opportunistic infection for idelalisib.

These defined adverse events make ibrutinib and idelalisib a priori unsuitable for patients who also have non-chronic lymphocytic leukaemia medical conditions that overlap with ibrutinib and idelalisib-related toxicities. Some of the adverse reactions may place certain groups of patients at risk for life-threatening events, e.g. patients on anticoagulation with anti-vitamin K for primary and secondary prevention of thromboembolic events (ibrutinib) and patients with autoimmune disorders, gastrointestinal dysfunction, compromised respiratory function or a history of opportunistic infection (idelalisib).

As it is of interest to understand the characteristics of patients with chronic lymphocytic leukaemia who fail a BCRi in NHS practice in England', no additional eligibility criteria are required.

3.4. It is estimated that approximately 20 new patients per month will be treated with venetoclax within the CDF during the managed access arrangement period.

3.5. In addition, there are approximately 100 existing patients who started venetoclax as part of the Early Access to Medicines Scheme between 23rd August 2016 and 5th December 2016 or AbbVie's 'free of charge' supply since the point of marketing authorisation (5th December 2016 until NICE guidance. If these patients can be identified within the Systemic Anti-cancer Therapy (SACT) dataset, Public Health England (PHE) will attempt to include them in the final analyses.

3.6. Treatment with venetoclax is until disease progression or no longer tolerated by the patient therefore, the average treatment duration is based on the time to disease progression.

- The average treatment duration is currently uncertain. As of the 10th June 2016 data cut, the median time on treatment for 158 patients was 17 months (range: 0 to 34 months) in the M13-982 trial with a median PFS of 27.2 months (range: 21.9-not reached). Median duration of treatment with venetoclax was 11.7 months (range: 0.1 to 17.9 months) in the M14-032 trial with a 12-month PFS of 72% (range: 56.6-82.4).

4. Area(s) of clinical uncertainty

4.1. The areas of clinical uncertainty are as follows:

- Venetoclax overall survival – patients for whom venetoclax would be an option in clinical practice in England have more advanced disease than patients in venetoclax clinical trials
- Venetoclax trials are all single-arm, and there is no comparative data in a matched population. As ibrutinib has been on the CDF, post-progression

survival data could be obtained from the SACT database. This would provide an approximation of best supportive care (BSC) in a population more relevant to clinical practice in England than either the company's or ERG's sources used in the appraisal.

5. Source(s) of data collection

5.1. It is anticipated that the key areas of clinical uncertainty will be addressed with information from the SACT dataset.

- Venetoclax. SACT will prospectively capture data on venetoclax use within the CDF. If patients can be identified, it is expected that SACT would also capture patients who initiated venetoclax as part of the EAMS program and the AbbVie 'free of charge' supply.

- Comparator BSC. It is anticipated that retrospective analyses using the SACT dataset will capture the use of BSC after the following treatments:

    - ibrutinib

    - idelalisib in combination with rituximab

- Providing that the follow-up is long enough, survival data may be available for patients on BSC following failure of ibrutinib or idelalisib in combination with rituximab.

5.2. The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. The SACT dataset will be the primary source of data collection. The SACT database routinely reports the data fields needed to answer the clinical uncertainty so no additional data items will be collected. The full data standard and data dictionary are available online.

6. Outcome data

6.1. Outcomes of interest are patients' time on treatment and overall survival along with baseline characteristics of patients included in the SACT dataset. It is noted that characteristics and prognostic factors will not be available for BSC.

6.2. Collection of time on treatment and overall survival for venetoclax will reduce the uncertainty associated with the extrapolation of the survival outcomes in AbbVie's submission.

6.3. Outcome data will also be collected for BSC (following failure to ibrutinib and idelalisib in combination with rituximab) as the comparator in the appraisal of venetoclax. Similarly to venetoclax, collection of time on treatment and overall survival for BSC in the NHS population in England will reduce the uncertainty associated with the extrapolation of the survival outcomes in AbbVie's submission. The availability and quality of retrospective data on BSC will be investigated to support data collection. However, older BSC data being collected routinely in SACT rather than current data linked to use within the CDF means that a difference in data quality is anticipated between venetoclax and BSC.

7. Data analysis plan

7.1. The SACT report will present anonymised summary data. Public Health England will aim to report:

Venetoclax:

- the total number of patients initiating treatment, patients' characteristics, overall survival, time on treatment
- PHE will investigate the possibility of reporting mean dose received; and, if patients received any other SACT regimen prior to meeting the eligibility criteria and receiving venetoclax (this will not include detail on what, if any, prior regimens were received or when they were received).

7.2. Analyses will be undertaken for the following populations:

a) all the venetoclax patients who entered the CDF,

b) the venetoclax patients who have failed a BCRi, with a split between those presenting or not with 17p deletion/TP53 mutation

c) the venetoclax patients presenting with 17p deletion/TP53 mutation and unsuitable for a BCRi.

BSC

- the total number of patients initiating treatment, overall survival, time on treatment

- PHE will investigate the possibility of reporting patients' characteristics; mean dose received; and, if patients received any other SACT regimen prior to meeting the eligibility criteria and receiving venetoclax (this will not include detail on what, if any, prior regimens were received or when they were received).

7.3. As highlighted in section 6.3, there will be a difference in past data availability and quality in data being collected routinely in SACT rather than current data for use with in the CDF.

7.4. It is anticipated that approximately 240 new venetoclax patients will be enrolled in the CDF during the 1st year, in addition to existing patients who started venetoclax as part of the EAMS program or AbbVie 'free of charge' supply. As hypotheses will not be tested and data from a naïve comparison between venetoclax and BSC will be incorporated into the economic model, it is AbbVie's position that in addition to the ~ 100 existing patients, the 240 new patients enrolled over 12 months and followed up for approximately 24 months should give confidence in the survival data for venetoclax and confidence in showing a difference in survival between BSC and venetoclax, because much lower survival is anticipated for the BSC comparator.

7.5. The number of patients who have received BSC following failure of ibrutinib or idelalisib in combination with rituximab is unknown.

7.6. PHE will attempt undertake an analysis of the data collected on venetoclax vs BSC in the SACT dataset. It is important to attempt to match the venetoclax and the BSC populations to ensure a fair comparison can be drawn. However it is AbbVie's understanding that limited demographic and prognostic factors

will be available for the comparator arm. AbbVie will therefore only be able to undertake a naïve comparison of venetoclax vs. BSC.

7.7. In order to attempt to match patients who received Venetoclax or BSC, PHE and NICE will explore the potential for this process to be undertaken.

7.8. Completeness of SACT dataset reporting will be shared with AbbVie on a quarterly basis. PHE will provide detailed results as highlighted in sections 6 and 7 at the end of the data collection period to AbbVie three months ahead of the planned review of NICE ID944.

8. Ownership of the data

8.1. SACT data is owned by individual patients, Public Health England is the data controller and will conduct analysis of SACT data. AbbVie will not have access to the SACT patient-level data but will receive the analysis (SACT report) that PHE produce at the end of the managed access period. Blueteq's CDF system data is owned by NHS England.

9. Publication

9.1. Publication of the analysis results of SACT data collected will be planned by PHE. AbbVie will be given access to the PHE report of the SACT dataset produced for the review of NICE technology appraisal guidance ID744 before the start of the review.

Commercial Access Agreement

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The contents of this document have been redacted as they are confidential

Single technology appraisal (STA)

Venetoclax for treating chronic lymphocytic leukaemia

Cancer Drugs Fund - Glossary of terms

Term	Explanation
Commercial access agreement	The standard way for pharmaceutical companies to make cancer drugs cost effective for the NHS either when they are recommended by NICE for entry into the Cancer Drugs Fund or if they were a transition drug in July 2016 and undergoing appraisal by NICE as a transition drug for exiting from the Cancer Drugs Fund. Each agreement is approved by NHS England.
Patient access scheme	The standard way for pharmaceutical companies to make cancer drugs cost effective for the NHS when they are routinely commissioned. Each scheme is approved by the Department of Health. Patient access schemes are part of the Pharmaceutical Price Regulation Scheme (2014)
Managed access agreement	A Cancer Drugs Fund managed access agreement consists of two components: · The first is a data collection arrangement, which sets out data that will be collected during the 'managed access' period to resolve clinical uncertainty · The second is a commercial access agreement that determines how much the NHS will pay for the treatment during the managed access period. This is normally a commercial access agreement that is managed by NHS England. However, if appropriate, a Department of Health-approved patient access scheme can also be used.