

Cancer Drugs Fund

Managed Access Agreement

**Ibrutinib for treating Waldenstrom's
macroglobulinaemia**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Managed Access Agreement - Foreword

Ibrutinib for treating Waldenström's macroglobulinaemia

This Managed Access Agreement (MAA) combines the agreed terms of the Data Collection Arrangement (DCA) and a confidential Commercial Access Agreement (CAA). It allows the entry to the Cancer Drugs Fund (CDF) of ibrutinib for treating Waldenström's macroglobulinaemia (WM).

The DCA outlines the agreed terms and responsibilities for additional data collection for the duration of the MAA. The data collection aims to resolve key uncertainties in the clinical evidence highlighted during the appraisal. The National Institute for Health and Care Excellence (NICE), Janssen, NHS England and Public Health England (PHE) have agreed that the primary source of additional data will be provided by the Systemic Anti-Cancer Therapy (SACT) dataset, supported by continued data collection in ongoing clinical trials. This is in line with [NICE's Specification for Cancer Drugs Fund data collection arrangements](#).

The [Guide to the methods of technology appraisal](#) states that, when possible, more than one independent source of studies without randomisation or control than those from RCTs should be examined to gain some insight into the validity of any conclusions. NICE is therefore encouraged that the patient and clinician jointly-led charity, WMUK, has developed the Rory Morrison Waldenström's Macroglobulinaemia UK Clinical Registry.

The NICE appraisal committee welcomes the efforts being made to collect data on this rare condition and its treatment. It heard that clinical data are being collected in the Rory Morrison Waldenström's Macroglobulinaemia UK Clinical Registry specifically from people with WM on outcomes including progression, survival, response, quality of life, and genomic markers. The committee considered that this data would be a valuable addition to the clinical evidence base and may resolve some of the uncertainties identified.

Upon the review of the guidance on ibrutinib for treating Waldenström's macroglobulinaemia at the end of the data collection period, NICE will accept the submission of all relevant evidence that can reduce clinical uncertainty and wishes to underscore that data sources do not need to be restricted to those named in the DCA.

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Cancer Drugs Fund – Data Collection Arrangement

Ibrutinib for treating Waldenström’s macroglobulinaemia (TA491)

Company name: Janssen

Primary source of data collection: Systemic Anti-Cancer Therapy

NICE Agreement Manager	Linda Landells, Associate Director – Technology Appraisals (Cancer Drugs Fund)
NHS England Agreement Manager	Peter Clark, CDF Clinical lead
Janssen Agreement Manager	Jennifer Lee, Health Economics, Market Access, Reimbursement & Advocacy Director
Public Health England Manager	Martine Bomb, Head of Data Projects, National Cancer Registration and Analysis Service

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 ibrutinib in the treatment of Waldenström’s macroglobulinaemia (TA491). A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee.

2 Commencement and period of agreement

- 2.1 Data will be collected over a three year period or until the jointly-agreed (between NICE, NHS England, and Janssen) commencement of the re-appraisal, whichever occurs first. An interim assessment, which will consider the findings of the quarterly reports described in Section 7.2, will be performed one year following the commencement of data collection; this assessment will inform the discussion that will jointly agree whether sufficient

data will be available for a re-appraisal after two years of data collection or whether the full three years are required. This data collection arrangement shall take effect on publication of the managed access agreement. The data collection period is anticipated to conclude three years from the date of the FAD publication or until the jointly-agreed commencement of the re-appraisal, whichever occurs first. 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 via 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 The population to be treated during the MAA period will be adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy and meet the inclusion/exclusion criteria described in the following sub-section. This is the population for which trial data are available and they represent a subpopulation of the marketing authorisation granted by the European Medicines Agency (EMA) which approves the use of ibrutinib in adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy (European Commission decision dated July 3rd 2015).
- 3.2 The patient eligibility criteria for treatment during the MAA period have been developed based on UK clinical opinion and in line with the Summary of Product Characteristics to ensure compliance and no off-label usage. The full criteria are as follows:
- i. 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

- ii. Confirmed clinicopathological diagnosis of Waldenström's Macroglobulinaemia (WM) and meeting criteria using consensus panel criteria from the Second International Workshop on WM (Owen et al 2003)
- iii. Documented progression of disease or no response to previous line of systemic therapy
- iv. Symptomatic disease meeting at least one of the recommendations for requiring active treatment as set out in the Second International Workshop on WM (Kyle et al 2003)
- v. Patient has received at least 1 prior line of treatment
- vi. Patient has never received any B cell receptor therapies (e.g. ibrutinib, acalabrutinib)
- vii. Ibrutinib is to be used as a single agent
- viii. Ibrutinib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
- ix. Performance status of the patient is 0 or 1 or 2
- x. Patient's neutrophil count is $\geq 1 \times 10^9/L$
- xi. Patient's platelet count $\geq 50 \times 10^9/L$
- xii. Patient is not on concurrent therapy with warfarin or CYP3A4/5 inhibitors
- xiii. No treatment breaks of more than 3 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)¹

¹ The standard additional time currently allowed by NHS England for toxicity to settle beyond the cycle length is now 6 weeks (previously 3 weeks). This change has been incorporated into NHS England's Blueteq criteria.

- xiv. Results of any gene testing in this patient are available (e.g. for MYD88)
 - xv. Ibrutinib to be otherwise used as set out in its Summary of Product Characteristics
- 3.3 The number of WM patients eligible for ibrutinib treatment as per the licence is estimated to be approximately 400 in year 1 (as there will be a bolus of patients awaiting treatment) and approximately 50 in year 2; of these, the number of patients expected to be eligible for ibrutinib that meet the eligibility criteria during the MAA period are estimated to be 265 in year 1 and 35 per year in years 2 and 3.
- 3.4 Ibrutinib is administered on a treat-to-progression basis. Median treatment duration has not been reached within Study 1118E at the 24-month follow-up data cut but the model extrapolations (as per the NICE submission) suggest median PFS will be met at approximately 36 months.

4 Area(s) of clinical uncertainty

- 4.1 The main clinical uncertainties identified in this appraisal which could be addressed within the MAA data collection period are pre-progression mortality in ibrutinib patients and treatment duration. With respect to pre-progression mortality in ibrutinib patients, given that only three deaths (all of which occurred pre-progression) were reported in Study 1118E over a median 14.8 months of follow-up and given the challenge of extrapolating a nearly flat survival curve, Janssen assumed in its initial NICE submission that ibrutinib survival was the same as in the general population. This was corroborated by expert clinical opinion. Following an ERG suggestion (Scenario analysis #3 in the ERG report), Janssen amended the model so that pre-progression mortality for ibrutinib was based on a constant hazard of projected Study 1118E overall survival data until this projection intersects with that of the general population mortality, at which point the general population mortality is applied. In its response to the ACD, Janssen rejected the scenario described by the ERG (Scenario analysis #7 in ERG report)

assuming “equivalent pre-progression mortality for the ibrutinib and comparator groups” on the basis that it is clinically implausible given the potency of ibrutinib. Further evidence is required to reduce the uncertainty around pre-progression mortality in WM patients treated with ibrutinib in the English clinical setting.

5 Source(s) of data collection

- 5.1 The primary source of data collection during the MAA period will be the Systemic Anti-Cancer Therapy (SACT) dataset. The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. The SACT database routinely reports some data fields needed to answer the clinical uncertainty. As such, SACT will be used to collect data on patient baseline characteristics, treatment duration and survival status.
- 5.2 As part of the guidance review, Janssen will provide supportive data from two clinical studies (the phase 2 registration Study 1118E and the phase 3 Study 1127 [iINNOVATE, arm C only]). Janssen has also signalled the intention to provide data from the disease-specific WMUK Rory Morrison Registry (see foreword to the MAA for more details).
- 5.3 Blueteq is a system routinely used by NHS England to manage prescribing of CDF funded medicines. Data will be collected via Blueteq alongside the primary source of data collection on demographics and characteristics of patients on ibrutinib for WM in clinical practice. NHS England is responsible for implementing Blueteq data collection and analysis. NHS England shares Blueteq data with Public Health England for CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

6 Outcome data

- 6.1 The following outcome data will be collected as follows by the sources outlined in Section 5 above:

- *Pre-progression mortality in ibrutinib patients:* The number of death events and time to death that occur while on treatment with ibrutinib.

These data will be collected via SACT. These data will be used to confirm the pre-progression mortality trend that has been reported from Study 1118E. Additional supportive data, as available, from longer-term follow-up of Study 1118E (n = 63) and arm C of Study 1127 (n = 31) will be provided.

- Patient baseline characteristics, treatment start and stop date, and survival status will be collected from the SACT database as the primary data source and supportive data will be taken from Study 1118E and Study 1127.

7 Data analysis plan

- 7.1 The SACT report will present depersonalised summary data, including the total number of patients initiating treatment with ibrutinib, survival and treatment duration (to be used as a proxy for progression) for all patients and those who die while still on treatment.

Proposed frequency of reporting

- 7.2 Completeness of SACT dataset reporting will be shared with Janssen on a quarterly basis. Public Health England (PHE) will provide summary results for time on treatment and survival to NHS England at the end of the data collection period, which will be shared with Janssen in advance of the planned review of guidance.

8 Ownership of the data

- 8.1 The data being collected via SACT is controlled by Public Health England (PHE). Janssen will not have access to the SACT patient-level data but will receive the analysis (SACT report) that PHE produce for NHS England at the end of the managed access period.
- 8.2 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. Individual patient data will remain within PHE premises and there will not be any data sharing of individual patient data outside of PHE. All necessary governance arrangements through SACT, and

other datasets brought together by PHE, have been established with NHS Trusts.

Source	Data Owner	General Data Governance Arrangements
Systemic Anti-Cancer Therapy (SACT) dataset	Public Health England (PHE)	<p>The data repository is hosted by the National Cancer Registration and Analysis Service (NCRAS) Oxford, (formerly the Oxford Cancer Intelligence Unit), and the data is held under their section 251 of the National Health Service Act 2006.</p> <p>Detailed technical guidance on the processes is available from the National Cancer Registration and Analysis Service in the Technical Guidance documents supporting the programme.</p>

9 Publication

- 9.1 Publication of the analysis results of SACT data collected will be planned by PHE. Janssen will be given access to the PHE report of the SACT dataset produced for NHS England for the review of NICE technology appraisal guidance (TA491) 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**