

Single Technology Appraisal

Ibrutinib for treating Waldenstrom's macroglobulinaemia (CDF Review of TA491) [ID3778]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

**Ibrutinib for treating Waldenstrom's macroglobulinaemia (CDF Review of
TA491) [ID3778]**

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491)

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1.	Professional organisation	BSH/ RCPATH	<p>Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?</p> <p>1. I agree with the clinical interpretations as detailed in the discussion however whilst SACT data is more generalisable to the UK population than the trial data, it is limited in its use due to the lack of information regarding response and duration of response. There is one publication to suggest that patients treated off trial (albeit at an academic centre with WM expertise) have similar outcomes to those treated on trial <i>Hemasphere 2020 e4(3): e363</i></p> <p>Probably the most granular data that is most generalisable is from the RMR database, however given that the majority of patients included in this registry that received ibrutinib off study have had it for a short period of time by definition, as it would have only been available when it became available in the CDF, then the follow up is too short to be able to interpret the durability of response and outcomes after discontinuation of ibrutinib.</p> <p>2. Estimating PFS for ibrutinib in the UK population. Patients will discontinue ibrutinib due to adverse events or due to progression. In the first instance, on discontinuation it will be variable how long patients will remain off treatment without disease progression. In the second situation, patients when they progress may not immediately discontinue treatment, and may stay on treatment for a period of time in the "progressed state" before proceeding to next treatment.</p>	<p>Thank you for your comments. The committee agreed that SACT data (and by extension data from the RMR database) was the most generalisable data to clinical practice in the NHS. the Limitations of these datasets were also acknowledged. No changes required.</p>

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			<p>Are the recommendations sound and a suitable basis for guidance to the NHS?</p> <p>I do not believe so, as this would be a big backward step in terms of treatment options for patients. Whilst many patients benefit from chemoimmunotherapy, repeated lines of chemoimmunotherapy leads to shorter responses, with increased risk of cumulative toxicities and risk of secondary malignancies. Ibrutinib is a very effective treatment option for patients with WM, and not having this available would be very difficult for patients and clinicians alike.</p>	<p>Thank you for your comment. The committee acknowledged that ibrutinib is a step-change in managing Waldenstrom's macroglobulinaemia. Its also noted the value of having a new and safe treatment option for treating Waldenstrom's macroglobulinaemia. No changes required.</p>
2.	Patient expert	-	<p>For me this is a real kick in the teeth. I was diagnosed with WM in 2001 at the age of 36, not the average age for this. I was treated in 2010 and 2015/16 and this was followed up with a stem cell transplant to give me a maximum treatment free period</p>	<p>Thank you for your comments. The committee noted</p>

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			<p>and in the hope that a BTK inhibitor would have been passed to be used for us by the time treatment is needed. My blood counts are now suggesting that treatment may be needed this year sometime. There have been almost 6 years of me not needing treatment and hence not costing the NHS, but now I feel as though there will be a fight on my hands again. I had to fight for my stem cell transplant to be completed in 2016 whilst you were contemplating the use of a preventative HIV treatment against others. That wasn't a good time.</p> <p>It feels as though WM, being rare, is almost forgotten about as we have no treatments directly aimed at us.</p> <p>Now it's likely I'll have to face the toxicity of further chemo, which in itself makes my risk of a 2nd cancer more likely, hence costing the NHS more. The joys of getting WM at a young age and needing treatment every few years I guess! I know imbruvica is expensive and money is limited, but it just feels like we don't matter 😞 Not good from a mental health point if view either</p>	<p>that ibrutinib is highly effective compared with existing treatments, and very well tolerated. It also acknowledged that ibrutinib is a step-change in managing a rare condition like Waldenstrom's macroglobulinaemia with many patients considering it to be a life-transforming drug that dramatically improves quality of life. No changes required.</p>
3.	Patient expert	-	<p>Just about all patients with WM are deemed by the Government as “clinically extremely vulnerable “which recognises the special nature of their immunosuppressant status. We accordingly are naturally very anxious in this new Covid world that will be with us for years to come if not indefinitely. So to have a “no” recommendation to a “game changer” drug like Ibrutinib is serving to only heighten our patient anxiety and that of family members.</p> <p>The current decision means that shortly, Ibrutinib will no longer be available to patients currently deemed suitable for its use, nor will anyone else be prescribed it. For a life transforming drug to be removed from the artillery of drugs to control WM seems like a “death sentence “to some and flies in the face of medical ethics I would argue - if it works, and it does (on all available clinical evidence) it should be made freely available to the benefit of thousands of people in England who need it.</p>	<p>Thank you for your comments. The committee noted that ibrutinib is highly effective compared with existing treatments, and very well tolerated. It also acknowledged that ibrutinib is a step-change in managing a rare condition like</p>

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			<p>Further, as the Cancer Drug Fund funding now ends it is cold comfort to those of us currently on Ibrutinib to hear that Janssen will fund the supply. They are a commercial enterprise and are at the mercy of market forces and unlike the NHS may make decisions that take the drug out of circulation with life changing and very likely early mortality for WM patients.</p> <p>The Scottish Medical Council have recently given Ibrutinib it's approval and so there is the ridiculous situation whereby in one part of the UK you can get Ibrutinib but in England you can't- it's absurd and an inequality that should not exist.</p> <p>Zanubrutinib has its NICE review shortly. It is a similar drug to Ibrutinib but cannot be viewed as a straight alternative as these targeted drugs are often tailored to patients needs and one may be totally unsuitable to replace the other and surely it is better for the Quality of life benefits (see the volume of positive testimony to this effect in the Committee's papers) to have more options available than less when dealing with a rare disease as WM is.</p> <p>Ibrutinib does offer to patients real hope that relapse is less likely than it is with toxic chemotherapy and thereby it reduces anxiety and being an oral drug taken at home the saving to the NHS in that many thousands of hospital visits are avoided must be colossal in a world where Covid remains a constant danger to life and health to all but in particular the population demographic who have WM (the elderly by and large).</p>	<p>Waldenstrom's macroglobulinaemia with many patients considering it to be a life-transforming drug that dramatically improves quality of life. No changes required.</p>

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4.	Company	Janssen-Cilag	<p>Introduction</p> <p>Janssen welcomes and thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for ibrutinib for treating patients with relapsed/refractory (RR) Waldenström’s macroglobulinaemia (WM) [ID3778].</p> <p>Overall, we are pleased that the Committee has acknowledged the “step-change” nature of ibrutinib in a disease with high unmet need and for which ibrutinib is the only licensed treatment available in the NHS, a position unanimously supported by patients and clinicians. Given this acknowledgement, we are disappointed with the provisional negative recommendation.</p> <p>Janssen recognises that despite four years of data collection, [REDACTED] some uncertainty remains. The residual uncertainty is due to the nature of the evidence base in a very rare condition where data for standard of care (SoC) in the UK is sparse at the time of the original appraisal and is now non-existent given ibrutinib has become SoC in WM second-line therapy. The residual uncertainty is also a consequence of the mutually agreed Cancer Drugs Fund (CDF) data collection arrangement (DCA) between NICE, Janssen and NHSE, which used the Systemic anti-cancer therapy (SACT) dataset as the primary data source, though SACT does not have the potential to collect data on progression-free survival (PFS) or</p>	<p>Thank you for your comments. Section 3.10 of the FAD has been updated to reflect that despite the high level of uncertainty in the exact extent of benefit of ibrutinib, the committee was satisfied that ibrutinib is a highly effective technology and it and an acceptable ICER would be comfortably below £30,000 per QALY gained but not at the upper limit, to reduce the risk of approving a cost ineffective treatment for use in the NHS</p>

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			<p>comparative effectiveness.</p> <p>We note that to enable ibrutinib exit from the CDF and the continuity of patient access to a life-changing treatment, the Committee has agreed on p15-16 of the ACD that “<i>an acceptable incremental cost-effectiveness ratio (ICER) would be around £20,000 per QALY gained</i>”, to reflect the “<i>high level of uncertainty</i>” identified in this re-appraisal. Janssen notes this is an exceptionally low ICER threshold for a step-change medicine in a very rare condition such as WM.</p> <p>Janssen strongly believes that this provisional recommendation is not a sound or suitable basis for guidance to the NHS, and that an acceptable ICER of around £30,000 per QALY gained is appropriate for a step-change medicine in a very rare condition. The reasons, which are further explained in the sections below, are the following:</p> <ul style="list-style-type: none"> (i) The choice of a £20,000/QALY threshold does not account for the social value of treating very rare diseases; (ii) The choice of a £20,000/QALY threshold goes against precedents of previous appraisals for rare diseases with high unmet need and the direction of travel of the recently published NICE guidance development manual¹ on greater acceptance of uncertainty in rare diseases and high unmet need conditions; (iii) The choice of a £20,000/QALY threshold does not account for aspects of health-related benefits and non-health factors that could not be accounted for in the ICER calculation; 	

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			<p>(iv) The wealth of evidence generated for ibrutinib in WM has significantly reduced and limited the remaining uncertainties (phase 2 trial follow-up, phase 3 randomised controlled trial (RCT), SACT and Rory Morrison Registry (RMR));</p> <p>(v) [REDACTED]</p> <p>Janssen remains fully committed to addressing the Committee's concerns and ensuring that patients continue to have access ibrutinib in RR WM.</p>	
5.	Company	Janssen-Cilag	<p>The choice of a £20,000/QALY threshold does not account for the social value of treating very rare diseases.</p> <p>NICE has repeatedly upheld a principle that there is a social value to treating very rare diseases, over and above their ordinary cost-effectiveness criteria. For example, treatments for ultra-orphan conditions may be assessed against thresholds of £100,000 or beyond via the highly specialised technology (HST) pathway. Ibrutinib for RR WM does not qualify for the HST pathway since ibrutinib is also used to treat other, more prevalent, blood cancers; yet the social value judgement on the importance of treating those unlucky enough to be diagnosed with a very rare condition nevertheless remains. Janssen consider, therefore, that an acceptable ICER of around £30,000 per QALY gained is appropriate for a step-change medicine for a very rare condition.</p>	<p>Thank you for your comments. Section 3.10 of the FAD has been updated to reflect that despite the high level of uncertainty in the exact extent of benefit of ibrutinib, the committee was satisfied that ibrutinib is a highly effective technology and it and an acceptable ICER would be comfortably below £30,000 per QALY gained but not at the upper limit, to</p>

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					reduce the risk of approving a cost ineffective treatment for use in the NHS
6.	Company	Janssen-Cilag	<p>The choice of a £20,000/QALY threshold goes against precedents of previous appraisals for rare diseases with high unmet need and the direction of travel of the recently published NICE guidance development manual² on greater acceptance of uncertainty in rare diseases and high unmet need conditions.</p> <p>NICE recently published a new guidance development manual which provides more clarity on how greater levels of uncertainty around the ICER may be acceptable for therapies which, like ibrutinib, are treating very rare disease, and for which by definition the clinical and economic evidence base is more uncertain.</p> <p>Section 6.2.34 of the new manual states that, though the committee will normally be more cautious about recommending a technology when they are less certain about the evidence presented, the committee will be mindful that there are certain technologies/populations for which evidence generation is particularly difficult because they are, for example, rare diseases or because the technologies are innovative and complex. In these specific circumstances, the new manual states that <i>“the committee may be able to make recommendations accepting a higher degree</i></p>		Thank you for your comments. The committee accepted that ibrutinib is a highly effective treatment option for Waldenstrom’s macroglobulinaemia. It noted that the current appraisal is not following the new methods set out in the new manual but acknowledged the difficulty in obtaining further new evidence for a rare condition like Waldenstrom’s macroglobulinaemia

² <https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation>

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			<p><i>of uncertainty”.</i></p> <p>There are already precedents, for example TA586, under the NICE old methods, where Committees have accepted higher ICERs/greater uncertainty because of unmet need/rarity. In TA586, lenalidomide plus dexamethasone is recommended despite a most plausible ICER above £30,000 per QALY. This flexibility was considered appropriate given multiple myeloma is an orphan condition and that there was an unmet need for an alternative option to toxic chemotherapy.</p> <p>Precedents, such as TA586, in conjunction with the clarification in the new manual around cases where Committees may be able to accept higher levels of uncertainty such as rare diseases, sustain Janssen’s belief that the appropriate threshold for this appraisal is around £30,000 per QALY. Ibrutinib as the first licensed treatment offering a step-change option for patients with a very rare disease, whose only alternative is off- label use of toxic chemotherapy (high unmet need), warrants at least as much flexibility as given to other rare conditions with high unmet need.</p>	<p>in section 3.10 of the FAD.</p>
7.	Company	Janssen-Cilag	<p>The choice of a £20,000/QALY threshold does not account for aspects of health-related benefits and non-health factors that could not be accounted for in the ICER calculation.</p> <p>Section 6.3.3 of the NICE Methods Guide³ lists five factors, all equally important, that will be considered for judgements about the acceptability of a technology as an effective use of NHS resources when the most plausible ICER is above £20,000 per QALY. Janssen considers that the following factors also mentioned in Section 6.3.3, should jointly be taken into account when judging</p>	<p>. Thank you for your comments. Section 3.10 of the FAD has been updated to reflect that despite the high level of uncertainty in the exact extent of benefit of ibrutinib, the committee was satisfied that</p>

³ <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781>

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			<p>whether ibrutinib is a cost-effective use of NHS resources:</p> <ul style="list-style-type: none"> • <i>“Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained;</i> • <i>The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure;</i> • <i>Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21)”. Section 6.2.20 further clarifies that these “non-health objectives” include situations where “a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services [...]” which is further detailed in Section 6.2.21.</i> <p>Uncaptured health-related benefits</p> <p>Janssen considers that not all ibrutinib health-related benefits have been captured in the QALY, and specifically:</p> <ul style="list-style-type: none"> (i) the peace of mind and the hope given to patients newly diagnosed with WM, with the knowledge that ibrutinib is an effective treatment with manageable safety profile available for them in second line. No utility was applied to the ibrutinib arm in the economic model to capture this psychological benefit in the QALY calculation. (ii) the convenient administration of ibrutinib as an oral therapy. The benefit of an oral administration was reported by the Committee in ACD Section 3.11 (p16) but was not deemed to be “enough” to increase the ICER threshold requested. 	<p>ibrutinib is a highly effective technology and it and an acceptable ICER would be comfortably below £30,000 per QALY gained but not at the upper limit, to reduce the risk of approving a cost ineffective treatment for use in the NHS</p> <p>Section 3.9 of the FAD notes that</p>

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			<p>Janssen notes that the benefit of an oral therapy taken in the comfort of one’s home goes beyond pure convenience and is critical in the context of a pandemic where alternative treatment options require a hospital visit, increasing patients’ anxiety level and level of logistics required to get effective access to WM treatment. EQ-5D scores are not sensitive to capture the benefits of convenience. Neither a utility associated with an oral therapy nor a disutility associated with intra-venous (IV) administration were applied in the respective ibrutinib and comparator arms of the economic model and were therefore accounted for in the QALY calculation.</p> <p>Uncaptured non-health factors (NHS resources savings)</p> <p>Oral administration of a treatment like ibrutinib is associated with significant resource-savings for the NHS; the value of this “convenience” benefit is critical during a pandemic, but also in the current post-pandemic situation, where oral therapies release further resources to treat the significant backlog of NHS cancer patients. In this case, the non-health benefit accrued by the wider NHS cancer patient community could not be captured in the ICER.</p> <p>Though Janssen has not quantified the NHS resource savings associated with treating WM patients with ibrutinib vs alternative IV therapies, the significant value to the NHS, in terms of saved staff time and reallocated facilities needed to manage WM patients with alternative therapies, both during the pandemic and post-pandemic period, cannot be overlooked.</p> <p>There are precedents, for example TA605, where an ICER in the region of £45,000 per QALY gained has been accepted. In TA605, health-related quality of life benefits are not fully captured in the QALY and limitation in how resource use was captured in the model were taken into consideration to make a positive</p>	<p>ibrutinib has several benefits including oral administration, manageable adverse reactions and low toxicity. It also notes the particular importance to people of being able to have treatment at home, reducing hospital visits, and acknowledges that the modelling did not capture the psychological benefit of having an effective treatment. However, the committee considered it likely that all the clinical benefits had already been included in the modelling.</p>

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			<p>recommendation despite the uncertainties and an ICER higher than £30,000 per QALY gained.</p> <p>Janssen believes that the ICER for ibrutinib in RR WM does not capture any of the utility/disutility or additional resource benefits mentioned above. Therefore, these additional health-related and non-health related benefits associated with ibrutinib should be accounted for by the Committee in their final recommendation for this appraisal.</p>	
8.	Company	Janssen-Cilag	<p>The wealth of evidence generated for ibrutinib in WM has significantly reduced and limited the remaining uncertainties (phase 2 trial follow-up, phase 3 RCT, SACT and RMR).</p> <p>The additional evidence generated over past four years has significantly reduced the uncertainty identified during the original appraisal (TA491).</p> <p>Evidence of ibrutinib effectiveness in WM at the time of license (2015) was very scarce - as commonly observed in the space of very rare diseases - and essentially limited to 24-month follow-up data from a phase 2 single arm US investigator-initiated study (IIS), Study 1118E. Hence despite the very promising results, there was still significant uncertainty around the clinical benefit of ibrutinib at the time, and specifically the relative benefit.</p> <p>The initial NICE submission (2016) was built around this IIS data. In the absence of any RCT, an indirect treatment comparison (ITC) of ibrutinib versus SoC (“physicians’ choice”) was conducted based on patient-level data (PLD) from the IIS and from a retrospective European chart review (ECR), funded by Pharmacyclics (co-developer of ibrutinib), to estimate ibrutinib’s relative PFS benefit.</p>	<p>Thanks you for your comments. Section 3.10 of the FAD has been updated to reflect that the committee understood the difficulty in obtaining further evidence for a rare condition like Waldenstrom’s macroglobulinaemia. Furthermore, the committee acknowledged that it was unlikely that any further analyses could resolve the uncertainty in the evidence base, or an alternative approach to</p>

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			<p>Some additional though very early survival data was also available from phase 3 iNOVATE arm C sub-study for ibrutinib monotherapy.</p> <p>The new and updated clinical evidence collected over the past four years as part of the CDF data collection has significantly reduced the uncertainty both by improving data maturity and by broadening the evidence base to the UK population:</p> <ul style="list-style-type: none"> • the trial evidence base includes an additional follow-up of 22 months and 41 months for pivotal phase 2 Study 1118E⁴ and iNOVATE arm C⁵ respectively, providing up to five years of PFS and overall survival (OS) data for each trial; • further trial data was also generated by Pharmacyclics/Janssen for the randomised arms of iNOVATE comparing ibrutinib and rituximab (I+R) versus rituximab in WM patients (n=150), with a total follow-up of 50 months⁶; • the trial evidence base was broadened with observational data from the SACT dataset, which included OS data from over 800 RR WM patients treated in NHS England; • SACT data was substantiated with additional PFS and OS data from a subset of 112 patients from the only UK WM-specific registry, the RMR. These data were collected at Janssen’s initiative. 	modelling could be suggested to reduce this uncertainty.

⁴ Treon *et al*, Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia, JCO, 2020 (<https://pubmed.ncbi.nlm.nih.gov/32931398/>)

⁵ Trotman *et al*, Single-Agent Ibrutinib for Rituximab-Refractory Waldenström Macroglobulinemia: Final Analysis of the Sub-study of the Phase III Innovate Trial, AACR Journals, 2021 (<https://pubmed.ncbi.nlm.nih.gov/34380643/>)

⁶ Buske *et al*, Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström’s Macroglobulinemia: Final Analysis from the Randomized Phase III iNOVATE Study, JCO, epub 2021 (<https://pubmed.ncbi.nlm.nih.gov/34606378/>)

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			<p>In the absence of PFS and comparative effectiveness data from SACT, Janssen acknowledges that some uncertainty remains with respect to the absolute and relative benefit of ibrutinib in UK clinical practice.</p> <p>Though some uncertainty remains, it is residual and inherent to (i) defining SACT as the primary data source and (ii) appraising any very rare disease such as WM.</p> <p>Defining SACT as the primary dataset for the CDF re-appraisal was a joint responsibility of all parties involved in the DCA including NICE, NHSE and Janssen. The fact SACT does not collect PFS data meant that a “structural” source of uncertainty would remain, both for ibrutinib’s absolute and relative benefit, that cannot be fully resolved. Janssen also notes that in practice it would have been impossible to collect comparative evidence for the re-appraisal given that ibrutinib has become SoC in the treatment of second line WM since it has become available through the CDF in 2017 and as reflected in the updated 2022 WM British Society for Haematology (BSH) guidelines.⁷</p> <p>Janssen strove to address some of the structural uncertainty for <u>ibrutinib absolute PFS benefit</u> through additional evidence generation to support this re-appraisal, which was challenging given the rarity of WM.</p> <p>First, Janssen collected ibrutinib PFS data from UK patients in the RMR (n=112) alongside PHE SACT data (n=823). Janssen considers the absolute PFS benefit of ibrutinib estimated in the model base-case is as close as possible to what the “true” ibrutinib PFS benefit would be in the SACT cohort given that that it was</p>	

⁷ Pratt *et al*, Guidelines on the diagnosis and management of Waldenström macroglobulinaemia—A British Society for Haematology guideline, BJH, 2022 (<https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.18036>)

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			<p>derived from PFS data from the RMR, which represents a subset of SACT.</p> <p>Second, Janssen also collected additional SACT time-to-next-treatment data presented in a Technical Engagement scenario to provide an upper boundary for ibrutinib SACT PFS, therefore reducing the uncertainty around the true PFS benefit of ibrutinib in the SACT cohort.</p> <p>Janssen maintains that the “true” <u>relative PFS benefit of ibrutinib</u> compared to Physicians’ Choice (PC) in the SACT cohort is not far from the HR=0.25 estimated by the ITC based on Study 1118E 24-month PLD and that was used in the CDF review base-case.</p> <p>In the absence of SACT PFS data, Janssen considers that the ITC HR is the most robust estimate to capture ibrutinib relative PFS benefit, given the new/updated evidence available: given no comparative trial data are available for ibrutinib vs PC, the ITC gives the most robust estimate for ibrutinib relative treatment benefit, because Study 1118E and the ECR are the datasets with the best overlap, especially for age, an established prognostic factor in WM.</p> <p>In addition, the results of the matched-adjusted indirect comparison (MAIC) presented by Janssen in a scenario as part of their Technical engagement response, and which was based on ibrutinib five-year follow-up data from Study 1118E, yielded a PFS HR of 0.28, consistent with the ITC HR of 0.25.</p> <p>Furthermore, clinicians attending the NICE first Appraisal Committee Meeting in December 2021 have all confirmed that a “low” PFS HR of 0.25, reflecting ibrutinib’s step-change nature compared to SoC, is clinically plausible.</p> <p>Lastly, the PFS HR observed in the phase 3 study iNNOVATE</p>	

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			<p>(n=150), which is a randomised controlled trial comparing IR versus rituximab in WM patients, is the same as in the ITC (HR=0.25); the PFS HR for the RR subset of WM patients is even lower (HR=0.22). Given I+R vs R is a robust randomised comparison capable of determining the relative benefit of ibrutinib, these results reinforce the robustness of the relative treatment effect modelled in the base-case.</p> <p>Given the evidence available, Janssen (and the ERG) have explored the limits of the remaining uncertainties around ibrutinib's absolute and relative PFS benefit; Janssen believes the magnitude of these is both residual and inherent to a rare disease.</p>	
9.	Company	Janssen-Cilag	<p>██</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>██</p> <p>.....</p>	Thank you for your comments. The comments relate to information which the committee were aware of but is not within the scope of this technology appraisal. No changes required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			----- ----- [REDACTED]	

Ibrutinib for treating Waldenström’s macroglobulinaemia (CDF Review of TA491) [ID3778]

Consultation on the appraisal consultation document – deadline for comments 5pm on Friday 11 February 2022. Please submit via NICE Docs.

<p>Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.</p> <p>The Appraisal Committee is interested in receiving comments on the following:</p> <ul style="list-style-type: none"> • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? <p>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:</p> <ul style="list-style-type: none"> • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. <p>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.</p>	
<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Janssen-Cilag</p>
<p>Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>N/A</p>
<p>Name of commentator person completing form:</p>	<p>*****</p>
<p>Comment number</p>	<p>Comments</p>
<p>1</p>	<p>Introduction</p>

Ibrutinib for treating Waldenström’s macroglobulinaemia (CDF Review of TA491) [ID3778]


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	<p>Janssen welcomes and thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for ibrutinib for treating patients with relapsed/refractory (RR) Waldenström’s macroglobulinaemia (WM) [ID3778].</p> <p>Overall, we are pleased that the Committee has acknowledged the “step-change” nature of ibrutinib in a disease with high unmet need and for which ibrutinib is the only licensed treatment available in the NHS, a position unanimously supported by patients and clinicians. Given this acknowledgement, we are disappointed with the provisional negative recommendation.</p> <p>Janssen recognises that despite four years of data collection, [REDACTED], some uncertainty remains. The residual uncertainty is due to the nature of the evidence base in a very rare condition where data for standard of care (SoC) in the UK is sparse at the time of the original appraisal and is now non-existent given ibrutinib has become SoC in WM second-line therapy. The residual uncertainty is also a consequence of the mutually agreed Cancer Drugs Fund (CDF) data collection arrangement (DCA) between NICE, Janssen and NHSE, which used the Systemic anti-cancer therapy (SACT) dataset as the primary data source, though SACT does not have the potential to collect data on progression-free survival (PFS) or comparative effectiveness.</p> <p>We note that to enable ibrutinib exit from the CDF and the continuity of patient access to a life-changing treatment, the Committee has agreed on p15-16 of the ACD that “<i>an acceptable incremental cost-effectiveness ratio (ICER) would be around £20,000 per QALY gained</i>”, to reflect the “<i>high level of uncertainty</i>” identified in this re-appraisal. Janssen notes this is an exceptionally low ICER threshold for a step-change medicine in a very rare condition such as WM.</p> <p>Janssen strongly believes that this provisional recommendation is not a sound or suitable basis for guidance to the NHS, and that an acceptable ICER of around £30,000 per QALY gained is appropriate for a step-change medicine in a very rare condition. The reasons, which are further explained in the sections below, are the following:</p> <ul style="list-style-type: none"> (i) The choice of a £20,000/QALY threshold does not account for the social value of treating very rare diseases; (ii) The choice of a £20,000/QALY threshold goes against precedents of previous appraisals for rare diseases with high unmet need and the direction of travel of the recently published NICE guidance development manual¹ on greater acceptance of uncertainty in rare diseases and high unmet need conditions; (iii) The choice of a £20,000/QALY threshold does not account for aspects of health-related benefits and non-health factors that could not be accounted for in the ICER calculation; (iv) The wealth of evidence generated for ibrutinib in WM has significantly reduced and limited the remaining uncertainties (phase 2 trial follow-up, phase 3 randomised
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¹ <https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation>

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	<p>controlled trial (RCT), SACT and Rory Morrison Registry (RMR);</p> <p>(v) </p> <p>Janssen remains fully committed to addressing the Committee’s concerns and ensuring that patients continue to have access ibrutinib in RR WM.</p>
<p>2</p>	<p>The choice of a £20,000/QALY threshold does not account for the social value of treating very rare diseases.</p> <p>NICE has repeatedly upheld a principle that there is a social value to treating very rare diseases, over and above their ordinary cost-effectiveness criteria. For example, treatments for ultra-orphan conditions may be assessed against thresholds of £100,000 or beyond via the highly specialised technology (HST) pathway. Ibrutinib for RR WM does not qualify for the HST pathway since ibrutinib is also used to treat other, more prevalent, blood cancers; yet the social value judgement on the importance of treating those unlucky enough to be diagnosed with a very rare condition nevertheless remains. Janssen consider, therefore, that an acceptable ICER of around £30,000 per QALY gained is appropriate for a step-change medicine for a very rare condition.</p>
<p>3</p>	<p>The choice of a £20,000/QALY threshold goes against precedents of previous appraisals for rare diseases with high unmet need and the direction of travel of the recently published NICE guidance development manual² on greater acceptance of uncertainty in rare diseases and high unmet need conditions.</p> <p>NICE recently published a new guidance development manual which provides more clarity on how greater levels of uncertainty around the ICER may be acceptable for therapies which, like ibrutinib, are treating very rare disease, and for which by definition the clinical and economic evidence base is more uncertain.</p> <p>Section 6.2.34 of the new manual states that, though the committee will normally be more cautious about recommending a technology when they are less certain about the evidence presented, the committee will be mindful that there are certain technologies/populations for which evidence generation is particularly difficult because they are, for example, rare diseases or because the technologies are innovative and complex. In these specific circumstances, the new manual states that <i>“the committee may be able to make recommendations accepting a higher degree of uncertainty”</i>.</p> <p>There are already precedents, for example TA586, under the NICE old methods, where Committees have accepted higher ICERs/greater uncertainty because of unmet need/rarity. In TA586, lenalidomide plus dexamethasone is recommended despite a most plausible ICER above £30,000 per QALY. This flexibility was considered appropriate given multiple myeloma is an orphan condition and that there was an unmet need for an alternative option to toxic chemotherapy.</p> <p>Precedents, such as TA586, in conjunction with the clarification in the new manual around</p>

² <https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation>

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	<p>cases where Committees may be able to accept higher levels of uncertainty such as rare diseases, sustain Janssen’s belief that the appropriate threshold for this appraisal is around £30,000 per QALY. Ibrutinib as the first licensed treatment offering a step-change option for patients with a very rare disease, whose only alternative is off-label use of toxic chemotherapy (high unmet need), warrants at least as much flexibility as given to other rare conditions with high unmet need.</p>
4	<p>The choice of a £20,000/QALY threshold does not account for aspects of health-related benefits and non-health factors that could not be accounted for in the ICER calculation.</p> <p>Section 6.3.3 of the NICE Methods Guide³ lists five factors, all equally important, that will be considered for judgements about the acceptability of a technology as an effective use of NHS resources when the most plausible ICER is above £20,000 per QALY. Janssen considers that the following factors also mentioned in Section 6.3.3, should conjointly be taken into account when judging whether ibrutinib is a cost-effective use of NHS resources:</p> <ul style="list-style-type: none"> • <i>“Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained;</i> • <i>The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure;</i> • <i>Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21)”. Section 6.2.20 further clarifies that these “non-health objectives” include situations where “a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services [...]” which is further detailed in Section 6.2.21.</i> <p>Uncaptured health-related benefits</p> <p>Janssen considers that not all ibrutinib health-related benefits have been captured in the QALY, and specifically:</p> <ol style="list-style-type: none"> (i) the peace of mind and the hope given to patients newly diagnosed with WM, with the knowledge that ibrutinib is an effective treatment with manageable safety profile available for them in second line. No utility was applied to the ibrutinib arm in the economic model to capture this psychological benefit in the QALY calculation. (ii) the convenient administration of ibrutinib as an oral therapy. The benefit of an oral administration was reported by the Committee in ACD Section 3.11 (p16) but was not deemed to be “enough” to increase the ICER threshold requested. Janssen notes that the benefit of an oral therapy taken in the comfort of one’s home goes beyond pure convenience and is critical in the context of a pandemic where alternative treatment options require a hospital visit, increasing patients’ anxiety level and level of logistics

³ <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781>

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	<p>required to get effective access to WM treatment. EQ-5D scores are not sensitive to capture the benefits of convenience. Neither a utility associated with an oral therapy nor a disutility associated with intra-venous (IV) administration were applied in the respective ibrutinib and comparator arms of the economic model and were therefore accounted for in the QALY calculation.</p> <p>Uncaptured non-health factors (NHS resources savings)</p> <p>Oral administration of a treatment like ibrutinib is associated with significant resource-savings for the NHS; the value of this “convenience” benefit is critical during a pandemic, but also in the current post-pandemic situation, where oral therapies release further resources to treat the significant backlog of NHS cancer patients. In this case, the non-health benefit accrued by the wider NHS cancer patient community could not be captured in the ICER.</p> <p>Though Janssen has not quantified the NHS resource savings associated with treating WM patients with ibrutinib vs alternative IV therapies, the significant value to the NHS, in terms of saved staff time and reallocated facilities needed to manage WM patients with alternative therapies, both during the pandemic and post-pandemic period, cannot be overlooked.</p> <p>There are precedents, for example TA605, where an ICER in the region of £45,000 per QALY gained has been accepted. In TA605, health-related quality of life benefits are not fully captured in the QALY and limitation in how resource use was captured in the model were taken into consideration to make a positive recommendation despite the uncertainties and an ICER higher than £30,000 per QALY gained.</p> <p>Janssen believes that the ICER for ibrutinib in RR WM does not capture any of the utility/disutility or additional resource benefits mentioned above. Therefore, these additional health-related and non-health related benefits associated with ibrutinib should be accounted for by the Committee in their final recommendation for this appraisal.</p>
5	<p>The wealth of evidence generated for ibrutinib in WM has significantly reduced and limited the remaining uncertainties (phase 2 trial follow-up, phase 3 RCT, SACT and RMR).</p> <p>The additional evidence generated over past four years has significantly reduced the uncertainty identified during the original appraisal (TA491).</p> <p>Evidence of ibrutinib effectiveness in WM at the time of license (2015) was very scarce - as commonly observed in the space of very rare diseases - and essentially limited to 24-month follow-up data from a phase 2 single arm US investigator-initiated study (IIS), Study 1118E. Hence despite the very promising results, there was still significant uncertainty around the clinical benefit of ibrutinib at the time, and specifically the relative benefit.</p> <p>The initial NICE submission (2016) was built around this IIS data. In the absence of any RCT, an indirect treatment comparison (ITC) of ibrutinib versus SoC (“physicians’ choice”) was conducted based on patient-level data (PLD) from the IIS and from a retrospective European chart review (ECR), funded by Pharmacyclics (co-developer of ibrutinib), to estimate ibrutinib’s relative PFS benefit. Some additional though very early survival data</p>

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	<p>was also available from phase 3 iNNOVATE arm C sub-study for ibrutinib monotherapy.</p> <p>The new and updated clinical evidence collected over the past four years as part of the CDF data collection has significantly reduced the uncertainty both by improving data maturity and by broadening the evidence base to the UK population:</p> <ul style="list-style-type: none"> • the trial evidence base includes an additional follow-up of 22 months and 41 months for pivotal phase 2 Study 1118E⁴ and iNNOVATE arm C⁵ respectively, providing up to five years of PFS and overall survival (OS) data for each trial; • further trial data was also generated by Pharmacyclics/Janssen for the randomised arms of iNNOVATE comparing ibrutinib and rituximab (I+R) versus rituximab in WM patients (n=150), with a total follow-up of 50 months⁶; • the trial evidence base was broadened with observational data from the SACT dataset, which included OS data from over 800 RR WM patients treated in NHS England; • SACT data was substantiated with additional PFS and OS data from a subset of 112 patients from the only UK WM-specific registry, the RMR. These data were collected at Janssen’s initiative. <p>In the absence of PFS and comparative effectiveness data from SACT, Janssen acknowledges that some uncertainty remains with respect to the absolute and relative benefit of ibrutinib in UK clinical practice.</p> <p>Though some uncertainty remains, it is residual and inherent to (i) defining SACT as the primary data source and (ii) appraising any very rare disease such as WM.</p> <p>Defining SACT as the primary dataset for the CDF re-appraisal was a joint responsibility of all parties involved in the DCA including NICE, NHSE and Janssen. The fact SACT does not collect PFS data meant that a “structural” source of uncertainty would remain, both for ibrutinib’s absolute and relative benefit, that cannot be fully resolved. Janssen also notes that in practice it would have been impossible to collect comparative evidence for the re-appraisal given that ibrutinib has become SoC in the treatment of second line WM since it has become available through the CDF in 2017 and as reflected in the updated 2022 WM British Society for Haematology (BSH) guidelines.⁷</p> <p>Janssen strove to address some of the structural uncertainty for <u>ibrutinib absolute PFS benefit</u> through additional evidence generation to support this re-appraisal, which was challenging given the rarity of WM.</p> <p>First, Janssen collected ibrutinib PFS data from UK patients in the RMR (n=112)</p>
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⁴ Treon *et al*, Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia, JCO, 2020 (<https://pubmed.ncbi.nlm.nih.gov/32931398/>)

⁵ Trotman *et al*, Single-Agent Ibrutinib for Rituximab-Refractory Waldenström Macroglobulinemia: Final Analysis of the Sub-study of the Phase III Innovate Trial, AACR Journals, 2021 (<https://pubmed.ncbi.nlm.nih.gov/34380643/>)

⁶ Buske *et al*, Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström’s Macroglobulinemia: Final Analysis from the Randomized Phase III iNNOVATE Study, JCO, epub 2021 (<https://pubmed.ncbi.nlm.nih.gov/34606378/>)

⁷ Pratt *et al*, Guidelines on the diagnosis and management of Waldenström macroglobulinaemia—A British Society for Haematology guideline, BJH, 2022 (<https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.18036>)

Comments on the ACD received from the experts

Name	Dima El-Sharkawi
Role	Clinical expert
Comments on the ACD:	
<p>Has all of the relevant evidence been taken into account? Yes</p> <p>Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?</p> <p>1. I agree with the clinical interpretations as detailed in the discussion however whilst SACT data is more generalisable to the UK population than the trial data, it is limited in its use due to the lack of information regarding response and duration of response. There is one publication to suggest that patients treated off trial (albeit at an academic centre with WM expertise) have similar outcomes to those treated on trial <i>Hemasphere 2020 e4(3): e363</i></p> <p>Probably the most granular data that is most generalisable is from the RMR database, however given that the majority of patients included in this registry that received ibrutinib off study have had it for a short period of time by definition, as it would have only been available when it became available in the CDF, then the follow up is too short to be able to interpret the durability of response and outcomes after discontinuation of ibrutinib.</p> <p>2. Estimating PFS for ibrutinib in the UK population. Patients will discontinue ibrutinib due to adverse events or due to progression. In the first instance, on discontinuation it will be variable how long patients will remain off treatment without disease progression. In the second situation, patients when they progress may not immediately discontinue treatment, and may stay on treatment for a period of time in the "progressed state" before proceeding to next treatment.</p> <p>Are the recommendations sound and a suitable basis for guidance to the NHS? I do not believe so, as this would be a big backward step in terms of treatment options for patients. Whilst many patients benefit from chemoimmunotherapy, repeated lines of chemoimmunotherapy leads to shorter responses, with increased risk of cumulative toxicities and risk of secondary malignancies. Ibrutinib is a very effective treatment option for patients with WM, and not having this available would be very difficult for patients and clinicians alike.</p> <p>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No</p>	

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<p>Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):</p>	<p>Individual patient expert</p>
<p>Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.</p>	<p>None</p>
<p>Name of commentator person completing form:</p>	<p>David Smith</p>
<p>Comment number</p>	<p style="text-align: center;">Comments</p> <p style="text-align: center;">Insert each comment in a new row.</p>

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that
1	Just about all patients with WM are deemed by the Government as “clinically extremely vulnerable” which recognises the special nature of their immunosuppressant status. We accordingly are naturally very anxious in this new Covid world that will be with us for years to come if not indefinitely. So to have a “no” recommendation to a “game changer” drug like Ibrutinib is serving to only heighten our patient anxiety and that of family members.
2	The current decision means that shortly, Ibrutinib will no longer be available to patients currently deemed suitable for its use, nor will anyone else be prescribed it. For a life transforming drug to be removed from the artillery of drugs to control WM seems like a “death sentence” to some and flies in the face of medical ethics I would argue - if it works, and it does (on all available clinical evidence) it should be made freely available to the benefit of thousands of people in England who need it.
3	Further, as the Cancer Drug Fund funding now ends it is cold comfort to those of us currently on Ibrutinib to hear that Janssen will fund the supply. They are a commercial enterprise and are at the mercy of market forces and unlike the NHS may make decisions that take the drug out of circulation with life changing and very likely early mortality for WM patients.
4	The Scottish Medical Council have recently given Ibrutinib its approval and so there is the ridiculous situation whereby in one part of the UK you can get Ibrutinib but in England you can’t- it’s absurd and an inequality that should not exist.
5	Zanubrutinib has its NICE review shortly. It is a similar drug to Ibrutinib but cannot be viewed as a straight alternative as these targeted drugs are often tailored to patients needs and one may be totally unsuitable to replace the other and surely it is better for the Quality of life benefits (see the volume of positive testimony to this effect in the Committee’s papers) to have more options available than less when dealing with a rare disease as WM is.
6	Ibrutinib does offer to patients real hope that relapse is less likely than it is with toxic chemotherapy and thereby it reduces anxiety and being an oral drug taken at home the saving to the NHS in that many thousands of hospital visits are avoided must be colossal in a world where Covid remains a constant danger to life and health to all but in particular the population demographic who have WM (the elderly by and large).

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under **‘commercial in confidence’ in turquoise** and all information submitted under **‘academic in confidence’ in yellow**. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: ‘academic / commercial in confidence information removed’. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright

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reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on the ACD received from the public through the NICE Website

Name	██████████
Role	
Comments on the ACD:	
<p>For me this is a real kick in the teeth. I was diagnosed with WM in 2001 at the age of 36, not the average age for this. I was treated in 2010 and 2015/16 and this was followed up with a stem cell transplant to give me a maximum treatment free period and in the hope that a BTK inhibitor would have been passed to be used for us by the time treatment is needed. My blood counts are now suggesting that treatment may be needed this year sometime. There have been almost 6 years of me not needing treatment and hence not costing the NHS, but now I feel as though there will be a fight on my hands again. I had to fight for my stem cell transplant to be completed in 2016 whilst you were contemplating the use of a preventative HIV treatment against others. That wasn't a good time.</p> <p>It feels as though WM, being rare, is almost forgotten about as we have no treatments directly aimed at us.</p> <p>Now it's likely I'll have to face the toxicity of further chemo, which in itself makes my risk of a 2nd cancer more likely, hence costing the NHS more. The joys of getting WM at a young age and needing treatment every few years I guess! I know imbruvica is expensive and money is limited, but it just feels like we don't matter</p> <p>😞 Not good from a mental health point if view either</p>	



Ibrutinib for treating Waldenström’s macroglobulinaemia (CDF Review of TA491) [ID3778]

Addendum: ERG comments on the company’s ACD response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Abdullah Pandor, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	22 nd February 2022

1. Introduction

In January 2022, the National Institute for Health and Care Excellence (NICE) issued its Appraisal Consultation Document (ACD) on the use of ibrutinib for treating Waldenström's macroglobulinaemia (WM).¹ The NICE ACD makes the following recommendation: "*Ibrutinib is not recommended, within its marketing authorisation, for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 prior therapy*" (NICE ACD,¹ Section 1.1, page 3).

The NICE ACD¹ highlights that there is uncertainty around the relative effectiveness of ibrutinib versus standard therapies in terms of progression-free survival (PFS) and overall survival (OS). The ACD also states that the incremental cost-effectiveness ratio (ICER) for ibrutinib versus standard therapies in people with WM is higher than what NICE usually considers a cost-effective use of NHS resources. The ACD suggests that owing to uncertainty around the relative effectiveness of ibrutinib versus standard therapies, "*an acceptable ICER is at the lower end of the acceptable range at around £20,000 per QALY gained.*" (NICE ACD,¹ Section 3.9, page 15).

In February 2022, the company submitted a written response to the NICE ACD.² The company's ACD response does not include any new clinical evidence or analyses. This addendum provides a brief commentary on the company's ACD response.

2. ERG comments on company's ACD response

The ERG's comments on the company's ACD response are summarised below.

(a) Appropriate threshold to use for decision-making

Most of the company's ACD response² relates to the appropriate cost-effectiveness threshold for decision-making. The company argues that it is appropriate to consider a threshold of around £30,000 per QALY gained for ibrutinib. The ERG believes that this is a matter for the Appraisal Committee to determine, rather than the ERG.

(b) Other health and non-health benefits not included in the model

The company's ACD response² argues that there are other health and non-health benefits which have not been captured in the company's cost-effectiveness estimates, but which are relevant for decision-making. These include benefits in terms of oral administration, convenience, and the avoidance of hospital visits for intravenous (IV) administration, as well as further indirect benefits to the NHS associated with releasing resources to treat the backlog of NHS cancer patients. The company's ACD response also mentions peace of mind and hope attributable to the availability of a safe and effective treatment for WM. The ERG believes that some of these factors might represent additional relevant benefits for ibrutinib and agrees that these are not explicitly captured in the company's economic

analyses. However, the company has not presented any evidence to support these claims or to quantify the magnitude of these additional benefits. In addition, Section 3.11 of the ACD¹ states that the clinical benefits of ibrutinib already appear to have been overestimated in the company's model. The ERG believes that the Appraisal Committee may wish to take account of some of these factors in a deliberative manner, but only if the other aspects of clinical benefit which are included in the model have not been overestimated.

(c) Uncertainty surrounding the relative effectiveness of ibrutinib

The company's ACD response² argues that “*the wealth of evidence generated for ibrutinib in WM has significantly reduced and limited the remaining uncertainties.*” However, as noted in the ACD,¹ there remains considerable uncertainty arising from: (i) the absence of data on PFS from the Systemic Anti-Cancer Therapy (SACT) database; (ii) the necessary reliance on estimates of relative treatment effects obtained from unanchored indirect treatment comparisons (ITCs); (iii) the indirect approach required to estimate outcomes for a SACT-like population receiving standard therapies and (iv) the lack of plausibility of the model predictions based on the company's original and updated ITCs. The ERG's concerns around these issues are discussed in detail in the ERG report³ and the ERG's technical engagement response;⁴ for brevity, these are not repeated here. In the absence of new supporting evidence and/or economic analyses, these concerns remain unchanged.

3. References

1. National institute for Health and Care Excellence. Ibrutinib for treating Waldenstrom's macroglobulinaemia - Appraisal Consultation Document. London, UK; 2022.
2. Janssen-Cilag. Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]. Company's response to the NICE ACD. London, UK; 2022.
3. Metry A, Tappenden P, Pandor A, Orr M. Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]. Sheffield, UK; 2021.
4. Metry A, Tappenden P, Ren K. Ibrutinib for Waldenström's macroglobulinaemia: A Cancer Drugs Fund review. ERG comments on the company's technical engagement response. Sheffield, UK; 2021.