National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Arsenic trioxide for treating acute promyelocytic leukaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Teva UK	no comment	Comment noted.
	BSH / RCPath	Yes	Comment noted.
Timing Issues	Teva UK	NHS England is currently undertaking an In-Year Service Development of arsenic trioxide for the treatment of APL, which is expected to be released later this year. In addition, appraisals by the Scottish medicines Consortium and All Wales Medicines Strategy are in process. As arsenic trioxide offers a potential cure for patients with APL, nationwide access should be considered a priority.	Comment noted. This topic is planned into the technology appraisals work programme
	BSH / RCPath	Moderately urgent. Patients already have access to highly successful first line chemotherapy options for APL but for first line therapy this appraisal will assess whether a chemotherapy-free option is possible thus minimising late effects of treatment. For those with relapsed refractory disease arsenic is already commissioned	Comment noted. This topic is planned into the technology appraisals work programme

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	NCRI-ACP-RCP	Our experts believe that it is very urgent as it gives patients with APL the opportunity of chemo-free curative therapy.	Comment noted. This topic is planned into the technology appraisals work programme
Additional comments on the draft remit	Teva UK	Any additional comments on the draft remit We consider that NICE should not pursue this Single Technology Appraisal for arsenic trioxide for the following reasons: • Arsenic trioxide is not a new therapy and is an established treatment for APL, with over 15 years' experience in the relapsed / refractory setting • NHS England are undertaking an In-Year Service Development of arsenic trioxide in the new indication (newly diagnosed low to intermediate APL; approved November 2016) and relapsed / refractory APL • The population eligible for arsenic trioxide as first-line therapy is very small and estimated to be 92 patients a year in England	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Teva UK	no comment	Comment noted.
	BSH / RCPath	The summary of leukaemia is fine **First Line Treatment** The treatment options is not in my view a fair assessment. There seems to be an implication that ATRA could be used as a single agent. I think it needs to be made very clear that this is not a standard of care and that, taking into	Comment noted. Scope updated accordingly

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		account patient fitness for treatment, ATRA is essentially always given with anthracyclines as part of the AIDA schedule There are some patients who get APL as a secondary cancer. Most of these have already received anthracycline and thus an AIDA approach cannot be safely delivered. This group may need special consideration as a group that would glean particular benefit from arsenic first line. To my knowledge this would already be the approach used nationally but perhaps via the IFR route. **Second Line Treatment** Arsenic is already commissioned as second line treatment in England. High dose chemotherapy and HSCT are not, in my view, reasonable comparators given the significant morbidity and mortality associated with these treatments and the very high cure rates with arsenic associated with low morbidity and mortality	
	NCRI-ACP-RCP	The background contains some omissions. Firstly although the standard current first line treatment for patients with APL is indeed chemotherapy with the AIDA regimen some patients with APIL are not suitable for chemotherapy, these include elderly patients and patients with secondary APL who have received previous chemotherapy and for these patients ATO (Trisenox) has been widely used although this may have to be by an IFR process. Also some centres may use 2 years maintenance chemotherapy after AIDA although this has generally fallen out of favour because it increases the risk of secondary MDS/AML Secondly for patients with either haematological or molecular relapse of APL (about 20% of patients overall) or who fail to remit on upfront chemotherapy (5-10% of patients) the standard 2nd line treatment has been routinely commissioned in the UK for several years is ATO combined with ATRA. For	Comment noted. Scope updated accordingly.

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		these patients 2nd line chemotherapy is not used although in some selected patients transplantation may be required after achieved of remission with ATO therapy.	
The technology/ intervention	Teva UK	no comment	Comment noted.
	BSH / RCPath	Yes	Comment noted.
	NCRI-ACP-RCP	Yes	Comment noted.
Population	Teva UK	In the scope document provided (Appendix B), the number of AML cases per year is reported as 2,590. We agree with this figure. However, arsenic trioxide is licensed only in adult patients (76.3% of the total population in the UK [1]), equating to 1,977 adult patients with AML. A US study looking at the incidence and survival of acute leukaemia between 2001 and 2007 noted that 7.4% of AML patients have APL [2]. This then calculates as 146 patients with APL (7.4% of 1,977). As first-line therapy, arsenic trioxide is licensed in patients with low to intermediate risk APL. Since 75.7% of patients have been reported to be at low to intermediate risk [3], this equates to 111 patients. In addition, early mortality is high with APL, with 83% survival at 30 days post diagnosis [4]. The population eligible for arsenic trioxide as first-line therapy is therefore estimated to be approximately 92 patients *per* year in England. [1] Office for National Statistics. Population estimates analysis tool. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesanalysistool [2] Dores GA, Devesa SS, Curtis RE, *et al*. Acute leukemia incidence and patient survival among children and adults in the United States, 2001–2007. *Blood* 2012;119:34–43	Comment noted. .

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		[3] Burnett AK, Russell NH, Hills RK, *et al*. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2015;16(13):1295–305 [4] Park JH, Qiao B, Panageas KS, *et al*. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. *Blood* 2011;118:1248–54	
	BSH / RCPath	It would strongly support children being included in this scoping. This group potentially has a lot to gain from omission of anthracyclines in terms of minimising late effects in a population that will have a long life expectancy and thus a long period to develop treatment-related adverse events. In addition of course to benefitting from improved long term remission rates after first treatment I would suggest that secondary APL may need separate consideration, particularly thinking of those patients who have had previous anthracycline therapy as outlined above	Comment noted. NICE will only appraise treatments within their marketing authorisation. Arsenic trioxide's marketing authorisation does not include use in children.
	NCRI-ACP-RCP	The population omits children with APL and there is a lot of interest in using ATO/ATRA treatment of APL in the paediatric population to avoid long term anthracycline toxicity. I think that children should be included in the scoping.	Comment noted. NICE will only appraise treatments within their marketing authorisation. Arsenic trioxide's marketing authorisation does not include use in children.

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Comparators	Teva UK	For patients with relapsed or refractory APL the alternative to arsenic trioxide is chemotherapy or transplant (not best supportive care). However, the use of second-line treatment will fall substantial if using arsenic trioxide during first-line treatment due to the limited number of patients failing treatment.	Comment noted. The comparators section of the scope has been updated.
	NCRI-ACP-RCP	As discussed above the standard 2nd line treatment has been routinely commissioned in the UK for several years is ATO combined with ATRA. For these patients 2nd line chemotherapy is not used although in some selected patients transplantation may be required after achieved of remission with ATO therapy BSC would rarely be used in APL except in very elderly frail relapsed patients. ATO is well tolerated in the elderly	Comment noted. The comparators section of the scope has been updated.
Outcomes	Teva UK	Other relevant outcomes include: • Relapse-free survival • Incidence of relapse (morphological and molecular) • Event-free survival / disease-free survival • Haematologic complete remission	Comment noted. Economic analysis is not limited to the outcomes provided in the scope, however results for these outcomes should be presented in the main analysis. Any analyses including other outcomes can be provided as part of your supplementary evidence.
	BSH / RCPath	Yes	Comment noted.

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		Molecular relapse should be considered given that there is evidence that intervention at the time of molecular relapse improves outcome	
	NCRI-ACP-RCP	Yes. Although PFS should include molecular relapse as well as haematologic relapse	Comment noted.
Economic analysis	Teva UK	A lifetime time horizon would be appropriate for economic analysis. In the APL0406 study, only 1 patient treated with arsenic trioxide died. A mortality rate of 0.8% (1/120) was calculated for arsenic trioxide [1]. [1] Platzbecker U, Avvisati G, Cicconi L, *et al*. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: Final results of the randomized Italian-German APL0406 trial. *J Clin Oncol* 2017;35:605–12	Comment noted.
	BSH / RCPath	The ATO schedule used in the UK AML 17 trial was different from that used in the licencing work but seemed equally efficacious. An broad costing was included in the AML 17 publication (Burnett et al Lancet Oncol 2015)	Comment noted.
	NCRI-ACP-RCP	NICE should be aware that in the UK the ATO used has been a different schedule to that in the SPC using a dose of ATO which is significantly less than used in other studies. This was part of the NCRI AML17 trial, a full economic case based upon the use of this schedule of ATO has been submitted to NHS England.	Comment noted.
Equality and Diversity	Teva UK	no comment	Comment noted.
	BSH / RCPath	Children are omitted and this should be given consideration	Comment noted. NICE will only appraise treatments within their marketing authorisation.

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		People who have secondary APL after a previous cancer need separate consideration	Arsenic trioxide's marketing authorisation does not include use in children.
	NCRI-ACP-RCP	Paediatric APL needs to be taken into account here. Also the requirement of older frailer patients with APL and secondary APL patients who are unsuitable for frontline chemotherapy and then special sub groups of patients such as those with Jehovah's witnesses for whom chemotherapy is not suitable and ATO as first line therapy offers a chance of cure which would otherwise not be available.	Comment noted. NICE will only appraise treatments within their marketing authorisation. Arsenic trioxide's marketing authorisation does not include use in children. Any equalities issues arising from Jehovah's witnesses religious beliefs will be taken into consideration.
Innovation	Teva UK	no comment	Comment noted.
	BSH / RCPath	I would consider the possibility of chemo-free treatment for APL to be a step change in practice	Comment noted.
	NCRI-ACP-RCP	The use ATO as front line therapy of APL instead of chemotherapy is a major innovation, it offers the chance of cure of this otherwise fatal leukaemia without the requirement for chemotherapy and the long term toxicities associated with it including long term cardiac toxicity. Furthermore requirements for supportive care are much reduced for patients' having ATO front line therapy compared to chemotherapy with a reduction in earlier death rate have a significant reduction in the risk of relapse.	Comment noted.

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Other considerations	Teva UK	The licensed indication for arsenic trioxide for newly diagnosed low to intermediate risk APL patients uses the dosing schedule from the APL0406 trial [1,2]. While Teva does not endorse off-label use of Trisenox, on the basis of information received from KoLs/experts/medical community, we are aware that they would wish to suggest alternative dosage regimens. [1] Lo-Coco F, Avvisati G, Vignetti C, *et al*. Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia. *N Engl J Med* 2013;369(2):111–21 [2] Platzbecker U, Avvisati G, Cicconi L, *et al*. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: Final results of the randomized Italian-German APL0406 trial. *J Clin Oncol* 2017;35:605–12	Comment noted.
Questions for consultation	Teva UK	***What diagnostic tests are needed to identify APL? If any, what costs (monetary and time) are associated with this diagnostic testing?*** Diagnostic tests include bone marrow biopsies and polymerase chain reaction (PCR) tests for diagnosing minimal residual disease (MRD). MRD monitoring is routinely used to guide therapy, with frequency of testing depending on choice of treatment ***Are the outcomes listed appropriate?*** See above ***Are there any subgroups of people in whom arsenic trioxide is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** No	Comment noted. Comment noted. Comment noted.

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		Do you consider arsenic trioxide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? ATRA + arsenic trioxide is a targeted therapy (specifically focussed at the degradation of the PML/RARα protein and to prevent its formation) in hemato-oncology bringing a potential cure.[1,2]	Comment noted.
		Arsenic trioxide provides a step-change in the management of APL. Administration of arsenic trioxide allows for the omission of the use of any chemotherapy in the frontline management of APL in patients with low-intermediate risk APL (white-cell count ≤$10x10^9$/L). It also offers a chemo-free alternative for patients requiring salvage therapy. The ability to cure patients with this aggressive form of cancer (early death rate within 30 days of diagnosis affects up to 17% of APL patients) [3] without chemotherapy could help to avoid unnecessary complications associated with chemotherapeutic agents, such as severe haematologic toxicity, a sizeable risk of toxic death and development of therapy-related malignancies. Furthermore, it has been suggested that molecular monitoring may not be required for patients treated with arsenic trioxide once molecular remission has been achieved as the relapse rate is extremely low. This is in contrast with the ATRA and chemotherapy schedule, where intensive minimal residual disease monitoring is required for 3 years, incurring an additional cost. [4] [1] Zhou G-B, Zhao W-L, Wang Z-Y, *et al*. Retinoic acid and arsenic for treating acute promyelocytic leukemia. *PLoS Med* 2005;2:e12 [2] Burnett AK, Russell NH, Hills RK, *et al*. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups	Comment noted.

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		(AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2015;16(13):1295–305 [3] Park JH, Qiao B, Panageas KS, *et al*. Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. *Blood* 2011;118:1248–54 [4] Personal correspondence with Prof Nigel Russell.	
		Where do you consider arsenic trioxide will fit into the existing NICE pathway, blood and bone marrow cancers? A new arm should be identified originating from the existing AML arm of the current pathway.	Comment noted.
		Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Arsenic trioxide offers clinical and resource use advantages over the comparators (see above)	Comment noted.
		Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? The primary outcomes are all still clinically relevant	Comment noted.
		Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? There are no new data/evidence for the comparators.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Janssen

Leukaemia care

Department of Health