National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia

Response to consultee and commentator comments on the draft remit and draft scope

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	Jazz Pharmaceuticals	Yes	Comment noted
	British Society for Haematology Royal College of Pathologists	May be useful to define 'high risk' in accordance with the license. VYXEOS is indicated for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	Comment noted. The remit wording is kept broad to be inclusive of the population covered by the marketing authorisation when it is granted. Liposomal cytarabine and daunorubicin will be appraised within its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Jazz Pharmaceuticals	NICE appraisal of the product is urgent: Existing methods of treatment of high-risk AML have significant limitations. Vyxeos will represent the first new treatment for 40 years which significantly improves overall survival in high-risk AML (as defined by therapy related AML or AML with myelodysplasia related changes) patients who are candidates for intensive chemotherapy, compared to standard of care '7+3'.	Comment noted.
Additional comments on the draft remit	Jazz Pharmaceuticals	We strongly recommend a scoping workshop to discuss the exact patient population relevant for treatment with Vyxeos.	Comment noted. A scoping workshop was not considered necessary for this topic.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Jazz Pharmaceuticals	Vyxeos is not intended for the treatment of all AML, but rather only for high-risk AML as defined by therapy related AML or AML with myelodysplasia related changes. There is a high unmet medical need for the treatment of the high-risk AML population.	Comment noted. The population section of the scope states that people must have high risk AML.
	British Society for Haematology Royal College of Pathologists	Accurate and succinct summary. Suggest remove red font. People who cannot tolerate or do not wish to receive intensive chemotherapy may have dose reductions or are given non-intensive chemotherapy such as low dose cytarabine[2]	Comment noted. This text has been removed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Leukaemia CARE	In Leukaemia CARE's recent 'Living with Leukaemia' survey – of 2,019 leukaemia patients, including 373 acute myeloid leukaemia (AML) patients, the most commonly reported AML symptoms were: • Fatigue (70%) • Feeling weak or breathless (56%) • Easily bruise or bleed (31%) • Fever / night sweats (26%) • Pain in bones / joints (24%) 'Living with Leukaemia' report available online at: http://www.leukaemiacare.org.uk/living-with-leukaemia (2,019 UK Leukaemia patients. Survey fieldwork conducted 26 September to 16 December 2016, published on 1st September 2017)	Comment noted. The background section of the scope is only intended to give a brief overview of the condition, its epidemiology and the treatment pathway. The symptoms, their impact on quality of life and the effect of treatment in alleviating symptoms will be considered during the appraisal.
The technology/ intervention	Jazz Pharmaceuticals	Brand name is known: Vyxeos Vyxeos is a unique and novel dual-drug liposomal technology combination of the antineoplastic drugs, cytarabine and daunorubicin, encapsulated in a sterile lyophilised liposome formulation – CombiPlex™ – for intravenous administration. The novel technology platform enables the optimised 5:1 molar ratio of cytarabine and daunorubicin encapsulated within a nano-scale bilamellar liposome to be delivered to the bone marrow and **preferentially taken up by leukaemic cells.**	Comment noted. The brand name has been added to the technology section of the scope. The technology section has been updated to state that liposomal cytarabine and daunorubicin is 'a liposomal encapsulated combination of cytarabine and

Section	Consultee/ Commentator	Comments [sic]	Action
		The 5:1 molar ratio has been shown in vitro to **maximise synergistic anti-tumour activity across multiple leukaemic and solid tumour cell lines, including AML**, and in animal model studies to be optimally efficacious compared to other cytarabine:daunorubicin ratios. Fixed ratiometric dosing represents a promising new approach to developing drug combinations. Systematically and simultaneously controlling the exposure of drug ratios using advanced nano-scale drug delivery vehicles can lead to prolonged maintenance of the optimal, synergistic ratio in leukaemic cells and exposure to tumours which in turn can provide statistically significant improvements in survival compared to free drug dosing. Vyxeos has been specifically developed to control the delivery and distinct individual pharmacokinetics of daunorubicin and cytarabine to optimise efficacy of treatment.	daunorubicin in a 5 to 1 molar ratio'.
	British Society for Haematology Royal College of Pathologists	Worth noting that the phase III randomized, open-label study of CPX-351 versus 7+3 (cytarabine plus daunorubicin) was in newly diagnosed patients with high-risk features- not all forms of AML.	Comment noted.
Population	Jazz pharmaceuticals	Our proposed indication is: Vyxeos is indicated as monotherapy for the treatment of adults with high-risk acute myeloid leukaemia (AML) as defined by therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). We highly recommend a scoping workshop to discuss the population relevant for treatment with Vyxeos.	Comment noted. The population section of the scope states that people must have high risk AML.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Haematology Royal College of Pathologists	As defined in the trial protocol.	Comment noted.
Comparators	Jazz Pharmaceuticals	Standard intensive therapy is an appropriate comparator, but note that Vyxeos was studied in both induction and consolidation in the phase III trial. Azacitidine is indicated for adult patients with AML that are not eligible for allogeneic HSCT, and so is not an appropriate comparator. We highly recommend a scoping workshop to discuss the population relevant for treatment with Vyxeos.	Comment noted. Consolidation therapy has been included in the comparators in the scope. The scope, including the comparators section, has been kept broad to ensure that it captures the whole of the possible marketing authorisation from the European Medicines Agency. A scoping workshop was not considered necessary for this topic.
	British Society for Haematology Royal College of Pathologists	Nearly- Daunorubicin and Cytarabine (DA 3 +7) is the international standard. Within the UK we utilise a '3 + 10'. The doses of Daunrobicin are the same (60mg/m2), however it is administered on days 1, 3 and 5 rather than the 1, 2 and 3 of a '3 + 7'. Similarly the cytarabine is given twice daily as IV 'push/bolus' for 10 days rather than a once daily continuous infusion for 7 days.	Comment noted. The technology section describes the dosing schedule used in the trial. Standard intensive therapy in the UK can

Section	Consultee/ Commentator	Comments [sic]	Action
		Within the current appraisal the comparator is predominantly DA- as the published studies are in the context of patients suitable for intensive chemotherapy. There is however significant interest in CPX-351 at reduced doses for patients not fit for intensive chemotherapy.	be defined over the course of the appraisal. The appraisal committee will consider the dose of liposomal cytarabine and daunorubicin that is anticipated to be covered by its marketing authorisation.
Outcomes	Jazz Pharmaceuticals	The pivotal phase III trial collected a wide range of efficacy, safety, PK, and resource use data. Disease-free survival was not formally captured as an endpoint. Our NICE submission will put the product's efficacy, safety, resource use and impact on QoL into the context of health-related benefits for England and Wales.	Comments noted.
	British Society for Haematology Royal College of Pathologists	The adverse effects should include an assessment of 30 and 60 day treatment related mortality, duration of hospitalisation.	Comments noted.
Economic analysis	Jazz Pharmaceuticals	Concerning time horizon, the base case analysis uses lifetime time horizon.	Comment noted.
Equality and Diversity	Jazz Pharmaceuticals	N/A	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Haematology Royal College of Pathologists	Copper Overload Reconstituted VYXEOS contains 5 mg/mL copper gluconate, of which 14% is elemental copper. There is no clinical experience with VYXEOS in patients with Wilson's disease or other copperrelated metabolic disorders.	Comment noted. Liposomal cytarabine and daunorubicin will be appraised within its marketing authorisation.
	Leukaemia CARE	As mentioned in the background, AML incidence correlates strongly with increasing age, with 66.9% of AML cases diagnosed in the over 65s. This has a number of implications – such as increased mortality (excess risk of death) and reduced likelihood of stem cell transplantation in the over 65s. Leukaemia CARE have produced a report looking at the challenges faced by older patients – entitled, 'Leukaemia: I wasn't born yesterday'. It is available online at: http://www.leukaemiacare.org.uk/i-wasnt-born-yesterday (1,305 leukaemia patients. A subsection of the Living with Leukaemia survey. Leukaemia: I wasn't born yesterday report published March 2017). As such, age related inequalities may arise during the process of this appraisal.	Comments noted. The scope does not define the population by age. The appraisal committee will consider any equality issues related to age during the appraisal.
Innovation	Jazz Pharmaceuticals	1. Jazz has applied for PIM designation and is currently arranging a meeting with the MHRA to discuss the outcome of the application. **As described above and below and in the PIM application, the technological innovation translated directly into health-related benefits.** • The 5:1 molar ratio of cytarabine:daunorubicin has synergistic cytotoxic effects on leukaemia cells in vitro and in vivo in tumour models	Comments on innovation noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Vyxeos is stable in the systemic circulation following intravenous infusion, releasing cytarabine and daunorubicin at a low rate and maintaining the synergistic 5:1 molar ratio of the two drugs for a prolonged period of time • Vyxeos appears to target and persist in the bone marrow • Vyxeos is taken up preferentially by leukemic vs normal bone marrow cells by an active engulfment process resulting in relatively selective cytotoxicity • Administered by 90-minute infusion • In a phase III, randomised, open-label, active-control trial, Vyxeos demonstrated superior overall survival and complete with a lower risk of early mortality compared to the '7+3' standard-of-care regimen in patients with high-risk AML 2. The benefit of Vyxeos is captured in the QALY of the economic model. 3. Our package for appraisal will include: • Vyxeos' clinical development history • A cost-effectiveness model • A systematic literature review • A network meta-analysis (if feasible) • A burden of illness review • A direct utility study	
	British Society for Haematology Royal College of Pathologists	Vyxeos utilizes CombiPlex® technology, which encapsulates a fixed ratio of drugs in a nano-scale delivery complex. Vyxeos received Breakthrough Therapy Designation from the FDA in May 2016 for the treatment of adults with therapy-related AML or AML with myelodysplasia-related changes. Vyxeos was also granted Fast Track Designation for the treatment of elderly	Comments noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		patients with secondary AML by the FDA, and Orphan Drug Designation by the FDA and the European Commission for the treatment of AML. The P3 data indicates, CPX-351 treatment resulted in superior overall survival (HR=0.69; P=0.005; median OS 9.56 vs. 5.95 months), EFS (HR=0.74; P=0.021), and CR+CRi response (47.7% vs. 33.3%; P=0.016). 60-day mortality favored CPX-351 (13.7% vs. 21.2%). Grade 3-5 AEs were equal (92% vs. 91%) and were similar in frequency and severity in both arms. (http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.7000) The allogeneic hematopoietic cell transplant (HCT) rate in patients aged 60-69 years was 37.5% in the CPX-351 arm and 32.4% in the 7+3 arm, with an OR of 1.25 (95% CI, 0.70-2.25). For patients aged 70-75 years, the allogeneic HCT rates were 28.1% and 11.1%, respectively, with an OR of 3.12 (95% CI, 1.12-8.72). (http://www.bloodjournal.org/content/128/22/902). Currently this data is available in abstract form only- ASCO and ASH 2016- as above. Various earlier phase studies have been published in different AML populations eg relapse and all primary AML.	
Other considerations	Jazz Pharmaceuticals	We recommend a scoping workshop.	Comment noted. A scoping workshop was not considered necessary for this topic.

Section	Consultee/ Commentator	Comments [sic]	Action
NICE Pathways [Delete section if not relevant]	Jazz pharmaceuticals	Within the NICE pathway, Vyxeos will be categorised under AML, with a population different from that of azacitidine.	Comment noted.
Questions for consultation	Jazz Pharmaceuticals	**Questions for consultation** *What clinical criteria are taken into account when deciding whether intensive chemotherapy is a suitable treatment for a person with acute myeloid leukaemia?* The determination of whether a patient is fit for intensive chemotherapy or not is a complex topic requiring a multi-disciplinary team approach. For the purposes of the phase III trial, the inclusion criteria specified an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. The ECOG performance status is an appropriate tool for assessing fitness. *How is high risk acute myeloid leukaemia defined?* Addressed above in 'Population': AML as defined by therapy related AML or AML with myelodysplasia related changes. *Have all relevant comparators for liposomal cytarabine and daunorubicin been included in the scope? Which treatments are considered to be established clinical practice in the NHS for newly diagnosed acute myeloid leukaemia?* Since 1973, the combination of cytarabine and an anthracycline has comprised the standard induction treatment phase (including in de novo AML, as well as secondary AML). While treatments vary to some extent, the '7+3'	Comment noted. Comment noted. Comment noted. Standard of care in the

Section	Consultee/ Commentator	Comments [sic]	Action
		regimen (which consists of cytarabine [100 to 200 mg/m^2/day] by continuous infusion on days 1 to 7 with daunorubicin [45 to 60 mg/m^2/day] on days 1, 2 and 3) is broadly considered standard of care across Europe with variations of this regimen, such as '3+10' or '3+8' in the UK (Horizon Scanning Vyxeos 2016). *Would liposomal cytarabine and daunorubicin be used as an alternative to azacitidine in the population for whom azacitidine is recommended in NICE technology appraisal guidance 218?* No, addressed above in 'Comparators'. *What consolidation therapy would be used following remission on liposomal cytarabine and daunorubicin? Would liposomal cytarabine and daunorubicin be used as a consolidation therapy following remission?* Yes, the phase III trial studied Vyxeos in both induction and consolidation. *Are the outcomes listed appropriate?* Addressed above in 'Outcomes'. *Are there any subgroups of people in whom liposomal cytarabine and daunorubicin is expected to be more clinically effective and cost effective or other groups that should be examined separately?* Vyxeos is clinically effective, and is expected to be cost-effective for a product with NICE End of Life status, in the entire phase III population.	UK will be defined during the appraisal. Comment noted. Comment noted. Comment noted. Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
		Where do you consider liposomal cytarabine and daunorubicin will fit into the existing NICE pathway, blood and bone marrow cancers? Within the NICE pathway, Vyxeos will be categorised under AML, with a population different from that of azacitidine. *Do you consider liposomal cytarabine and daunorubicin 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)?* Addressed above under 'Innovation'. *Do you consider that the use of liposomal cytarabine and daunorubicin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* Addressed above under 'Innovation'. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Addressed above under 'Innovation'. *To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.* We do not anticipate any barriers to adoption. In a phase III, randomised, open-label, active-control trial, Vyxeos demonstrated superior overall survival	Comment noted. Comments on innovation noted. Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		and complete response with a lower risk of early mortality compared to the '7+3' standard-of-care regimen in patients with high-risk AML. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).* *NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic.* *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?* In terms of clinical efficacy, in the phase III trial, Vyxeos was shown to be superior to the standard of care comparator ('7+3'). In terms of resource use, Vyxeos is delivered by a 90-minute intravenous infusion, as compared to five- or seven-day continuous infusion of cytarabine in current induction and consolidation therapy. *Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?* Yes. The primary endpoint of the phase III trial was overall survival.	Comment noted. NICE has not appraised the cost effectiveness of standard intensive induction. Cost comparison methodology is not applicable to a comparison with standard intensive induction therapy.

Section	Consultee/ Commentator	Comments [sic]	Action
		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? **The standard of care was first developed 40 years ago. While the SoC is still studied in the context of clinical protocols, no important changes in efficacy are expected to be demonstrated in the next year.**	
	British Society for Haematology Royal College of Pathologists	Consideration is required for the ability and availability for pumps for the continuous infusion required for administration. Increased incidence of G3/4 neutropenia and thrombocytopenia with Vyxeos-significance and outcome unclear.	Comments noted. Resource use, costs and adverse events will be considered over the course of the appraisal.
Additional comments on the draft scope	Jazz Pharmaceuticals	Our proposed indication is: Vyxeos is indicated as monotherapy for the treatment of adults with high-risk acute myeloid leukaemia (AML) as defined by therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). We highly recommend a scoping workshop to discuss the population relevant for treatment with Vyxeos.	Comment noted. Comment noted. A scoping workshop was not considered necessary for this topic.

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

Department of Health and Social Care