Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2181

arsenic trioxide 1mg/mL concentrate for solution for infusion (Trisenox®)

Teva UK Ltd

7 June 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

arsenic trioxide (Trisenox®) is accepted for use within NHSScotland.

Indication under review: in combination with all-*trans*-retinoic acid (ATRA [tretinoin]) for the induction of remission, and consolidation in adult patients with newly diagnosed, low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count ≤10 x 10^3/µl), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.

In a Phase III study in patients with newly diagnosed, low-to-intermediate risk APL, arsenic trioxide was non-inferior to anthracycline-based chemotherapy (both in combination with tretinoin) measured by event-free survival. A significant difference in overall survival favouring arsenic trioxide was also demonstrated.

Chairman
Scottish Medicines Consortium

Indication

In combination with all-trans-retinoic acid (ATRA [tretinoin]) for the induction of remission, and consolidation in adult patients with newly diagnosed, low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count ≤10 x 10^3/µl), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.[1]

Dosing Information

Newly diagnosed low-to-intermediate risk APL:

Induction treatment schedule

Administered intravenously at a dose of 0.15mg/kg/day, given daily until complete remission is achieved. If complete remission has not occurred by day 60, dosing must be discontinued.

Consolidation schedule

Administered intravenously at a dose of 0.15mg/kg/day, 5 days per week. Treatment should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles.

Arsenic trioxide must be administered intravenously over 1 to 2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. Patients must be hospitalised at the beginning of treatment due to symptoms of disease and to ensure adequate monitoring.

Treatment with arsenic trioxide must be temporarily interrupted before the scheduled end of therapy at any time that a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed and judged to be possibly related to arsenic trioxide treatment. Patients who experience such reactions that are considered arsenic trioxide related must resume treatment only after resolution of the toxic event or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50% of the preceding daily dose. If the toxic event does not recur within seven days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment.

Arsenic trioxide should be administered under the supervision of a physician who is experienced in the management of acute leukaemias and the special monitoring procedures must be followed.

Full details are provided in the Summary of Product Characteristics. [1]

Product availability date

13 October 2016

Arsenic trioxide meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Arsenic trioxide is an antineoplastic agent, but its mechanism of action in acute promyelocytic leukaemia (APL) is not fully understood. In vitro, arsenic trioxide causes DNA fragmentation characteristic of programmed cell death in human promyelocytic leukaemia cells, and it is also known to damage promyelocytic leukaemia/retinoid acid receptor-alpha (PML/RAR-alpha). [1]

APL is a rare subtype of acute myeloid leukaemia which progresses rapidly.[2, 3] This subtype is characterised by a translocation between chromosomes 15 and 17, fusing the PML/RAR-alpha gene, though variant translocations are possible (for example t11;17 PLZF/RAR-alpha). Anthracycline-based chemotherapy (usually idarubicin), in combination with all-*trans*-retinoic acid (tretinoin) is currently used as first-line treatment.[3-5]

This submission is for the license extension to first-line use of arsenic trioxide for induction of remission and consolidation in adult patients with newly diagnosed low-to-intermediate risk APL (white blood cell count ≤10 x 10^9/L) in combination with tretinoin. Arsenic trioxide has been available since 2002 to treat relapsed or refractory APL.

Key evidence for this indication comes from APL0406, a phase III, open-label, randomised, non-inferiority study. Eligible patients were 18 to 71 years of age, with newly diagnosed genetically confirmed APL classified as low-to-intermediate risk (white blood cell [WBC] count ≤10x10^9/L), with World Health Organisation (WHO) Performance Status ≤2, creatinine ≤265 micromol/L and bilirubin ≤51 micromol/L. To prevent treatment initiation delays, patients could be randomised on the basis of morphologic diagnosis only, before the results of genetic tests were available. A protocol amendment increased the target sample from 162 to 276 (the extended cohort) to reach an optimal compliance with quality of life questionnaires (a secondary endpoint).[3]

Patients were randomised to receive either arsenic trioxide plus tretinoin, or idarubicin plus tretinoin (stratified by institution). Patients randomised to arsenic trioxide received induction with arsenic trioxide 0.15mg/kg and tretinoin 45mg/m^2 daily until complete remission for a maximum of 60 days, followed by consolidation with arsenic trioxide five days a week (four weeks on, four weeks off, for four cycles) and tretinoin (two weeks on, two weeks off, for seven cycles).

Patients randomised to idarubicin received induction with idarubicin 12mg/m^2/day (on days 2, 4, 6 and 8) and tretinoin 45mg/m^2/day until remission for a maximum of 60 days, followed by three one month cycles of anthracycline-based chemotherapy (idarubicin in Cycles 1 and 3; mitoxantrone in Cycle 2) with tretinoin 45mg/m^2/day on days 1 to 15 of each cycle. Maintenance therapy (consisting of intramuscular or oral methotrexate 15mg/m^2 weekly, 6-mercaptopurine 50 mg/m^2/day, and tretinoin 45mg/m^2/day for 15 days every three months) for up to two years was then given to patients who tested negative for promyelocytic leukaemia/retinoic acid receptor alpha at recovery from the third cycle of consolidation therapy.[3, 6]

Prednisone 0.5mg/kg/day was administered to all patients from day 1 until the end of induction therapy as prophylaxis for differentiation syndrome.[3, 6] Arsenic trioxide, tretinoin or both were temporarily withheld and prednisolone was switched to dexamethasone 10mg every 12 hours if differentiation syndrome was suspected, for a minimum of three days until signs and symptoms resolved. Hydroxycarbamide could be given to patients who developed leucocytosis (discontinued once WBC count <10x10^9/L).[3]

The primary outcome was the difference between the two groups in rates of event-free survival two years after diagnosis, that is the time from the date of randomisation to the date of first documentation of treatment failure. A non-inferiority analysis (pre-specified margin of -5%) was carried out in 229 patients with sufficient follow up (beyond 24 months): event-free survival was 98% and 86% in the respective groups (95% confidence interval [CI] for the difference 4.3% to 20%, thus non-inferiority was confirmed). In the extended cohort (n=263 evaluable for ITT analysis), after median follow up of 40.6 months, the two-year event-free survival rates (calculated from Kaplan-Meier curve) were 98% and 87%, and 50-month event-free survival rates were 97% and 80%, in the arsenic trioxide and idarubicin groups, respectively (p<0.001).[7]

Results for key secondary outcomes are summarised in Table 1 below for the extended cohort.

Table 1: Summary of key secondary efficacy endpoints for the extended cohort (estimated from Kaplan-Meier curves).[3, 7]

	arsenic trioxide + tretinoin	**idarubicin + tretinoin**	p-value
2-year overall survival	99%	95%	p=0.0073
50-month overall survival	99%	93%	
2-year disease-free survival	98%	89%	p<0.001
2-year cumulative incidence of relapse	0.9%	8.2%	p=0.0013
50-month cumulative incidence of relapse	1.9%	14%	

Health-related quality of life (HR-QoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). Fatigue severity was significantly lower after induction therapy in patients randomised to arsenic trioxide compared with patients randomised to idarubicin (p=0.034 and p=0.008 in the original and extended cohorts, respectively).[3, 7]

AML17 was a phase III, multicentre, randomised, open-label study comparing arsenic trioxide plus tretinoin with idarubicin (mitoxantrone in course 3) plus tretinoin in low-to-intermediate risk and high-risk adult patients (n=235, lower than the target recruitment of 300 patients thus limiting the power of the study) with APL. Only the low-to-intermediate risk population (76% of the total study population) is relevant to the indication under review. Eligible patients were at least 16 years of age having received no previous treatment for APL, and the presence of the PML/RAR-alpha transcript had to be confirmed by a reference laboratory. The dosing regimen for arsenic trioxide

plus tretinoin in AML17 was not the licensed dosing schedule.[3, 8] No maintenance phase was planned for either group and CNS prophylaxis was not given.[8]

In AML17, the primary outcome was HR-QoL assessed by EORTC QLQ-C30. All analyses were in the ITT population.[8] Results were based on a median follow-up of 30.5 months. Study AML17 did not meet its primary objective as quality of life did not differ significantly between the treatment groups (EORTC QLQ-C30 global functioning effect size). The only domains of the EORTC QLQ-C30 in which there were statistically significant differences between the treatment groups was cognitive and role functioning, which favoured arsenic trioxide plus tretinoin.[8] In the low- to intermediate-risk patients, 4-year event-free survival was 92% in the arsenic trioxide plus tretinoin group versus 71% [in the idarubicin plus tretinoin group (HR=0.34; 95% CI [0.15 to 0.75], p=0.008) and 4-year overall survival was 95% in the arsenic trioxide plus tretinoin group versus 90% in the idarubicin plus tretinoin group (HR=0.47; 95% CI [0.16 to 1.39]).[3]

Summary of evidence on comparative safety

Safety data have been reported for the extended cohort from APL0406 as this was the final analysis and included all enrolled patients. Sixty five patients reported a total of 95 serious adverse events (43 events and 52 events in the arsenic trioxide and idarubicin groups, respectively).[7]

A significantly lower proportion of patients in the arsenic trioxide arm than in the idarubicin arm experienced haematologic adverse events during induction (p<0.001 for all comparisons): grade 3 or 4 neutropaenia lasting more than 15 days (35% versus 64%, respectively); grade 3 or 4 thrombocytopaenia lasting more than 15 days (38% versus 62%); and infection and fever of unknown origin (23% versus 55%). Similar results were observed during consolidation phases, with the exception of infection and fever of unknown origin during first consolidation which was experienced by 8% and 6% of patients in the respective groups and third consolidation by 1.6% and 1.7% (differences were not significant).[7]

Of the non-haematological events, grade 3 to 4 hepatic toxicity was more common among patients in the arsenic trioxide group compared with patients in the idarubicin group. During induction a statistically significant difference was observed (40% versus 3%, p<0.001). Hepatic toxicity resolved in all cases with temporary discontinuation of arsenic trioxide and/or tretinoin or of low-dose chemotherapy during maintenance. Grade 3 to 4 QTc prolongation was more common among patients in the arsenic trioxide group compared with patients in the idarubicin group across all treatment cycles, with the difference reaching significance during induction (8.5% versus 0.7%, p=0.0022). Neurotoxicity was significantly more common in the arsenic trioxide group during the consolidation phases than in the idarubicin group (4.2%, 5% and 5.9% in the arsenic trioxide group in the first, second and third consolidation cycles versus 0% in the idarubicin group). However, gastrointestinal toxicity was significantly less common in patients treated with arsenic trioxide than in those given idarubicin during induction (2% versus 18%, p<0.001) and second

consolidation (0% versus 4.9%, p=0.03). There were no cases of secondary leukaemia in the arsenic trioxide group compared with two cases in the idarubicin group. [7]

Severe differentiation syndrome was reported in five patients (4%) and eight patients (6%) in the arsenic trioxide and idarubicin groups, respectively. Two of the cases in the idarubicin group were fatal.[3] The SPC for arsenic trioxide notes that differentiation syndrome is a very common adverse event.[1] Differentiation syndrome has also been reported in patients with APL taking tretinoin.[3]

Nine serious adverse events had a fatal outcome. Of these, five were considered to be related to study treatment: one case of acute respiratory distress syndrome (ARDS) related to tretinoin and idarubicin; one case of respiratory failure and retinoic acid syndrome related to tretinoin and idarubicin; one case of ischemic stroke related to tretinoin and idarubicin; one case of bronchopneumonia considered related to tretinoin; and one case of bronchopneumonia considered related to methotrexate.[3]

Summary of clinical effectiveness issues

APL is a subtype of acute myeloid leukaemia, accounting for approximately 10% of cases.[3] Symptoms include bruising and bleeding, and rapid initiation of treatment is essential upon diagnosis because it is considered a haematological emergency.[2] There is a high cure rate for APL, estimated at approximately 80% however around 10% of patients die early.[3] Arsenic trioxide meets SMC orphan equivalent criteria.

In study APL0406, a statistically significant difference was observed between treatment groups with a higher proportion of patients randomised to arsenic trioxide plus tretinoin compared with patients randomised to idarubicin plus tretinoin being event-free at two years and at 50 months. The EMA concluded that the primary outcome results of APL0406 were of high clinical relevance as the majority of relapses in APL occur within 2 years of response being achieved. Furthermore, overall survival at 50 months was significantly greater in the arsenic trioxide plus tretinoin group than in the idarubicin plus tretinoin group, and the cumulative incidence of relapse at 50 months was significantly lower in the arsenic plus tretinoin group than in the idarubicin plus tretinoin group.[3, 7]

Given the differences in dosing regimens between the treatment arms, both the APL0406 and AML17 studies were open label. In APL0406 a protocol amendment increased the target sample size when compliance with HR-QoL in the initial cohort of enrolled patients was observed to be lower than expected and considered insufficient to perform the planned analysis.[3] In study AML17 arsenic trioxide was not given at the licensed dose.[8] However the EMA notes that 'no formal dose-response study was conducted to investigate the optimal dose and schedule for *[arsenic trioxide]* when used in combination with *[tretinoin]*'.[3] Patients >71 years old were excluded from APL0406. There was no upper age limit in the AML17 study but there was no specific description of efficacy in an elderly population.[3]

Study AML17 did not meet its primary objective as quality of life did not differ significantly between the treatment groups.[3, 8] Patients in the idarubicin group in AML17 were not given maintenance treatment. Maintenance treatment was given in the idarubicin group in APL0406.[3]

Arsenic trioxide in combination with tretinoin would provide an alternative treatment option in first-line management of APL in the population of patients with low-to-intermediate risk disease. Clinical experts consulted by SMC considered that arsenic trioxide is a therapeutic advancement due to being an alternative to chemotherapy with potentially superior efficacy.

The SPC states that patients should be hospitalised at the beginning of treatment with arsenic trioxide due to symptoms of disease and to ensure adequate monitoring. Electrolyte and glycaemia levels, as well as haematologic, hepatic, renal and coagulation parameter tests must be monitored at least twice weekly, and more frequently for clinically unstable patients during the induction phase and at least weekly during the consolidation phase.[1] Clinical experts considered that the introduction of this treatment may reduce hospital inpatient stay but require more outpatient visits than chemotherapy.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing arsenic trioxide plus tretinoin to idarubicin plus tretinoin for the treatment of patients with newly diagnosed low-to-intermediate risk APL (white blood cell count, ≤10 x 10^9/L). Based on SMC expert responses idarubicin plus tretinoin appears to be the comparator most likely to be displaced in practice.

The company submitted a 14-state Markov model which follows patients newly diagnosed with low-to-intermediate risk APL from their first-line treatment induction to treatment consolidation. The time horizon used in the analysis was 40 years. Molecular remission and longer term remission following first-line treatment are built in as tunnel states. Cardiac events prompt a treatment switch where patients move to the second-line induction and consolidation therapies. This health state consisted of ten tunnel states, allowing the consolidation phase to comprise up to five treatment cycles (induction and then consolidation) and for second-line molecular remission. Cardiac adverse events prompt second-line treatment discontinuation and then patients would undergo a hematopoietic stem cell transplant (HSCT). Both allogeneic stem cell transplant (SCT) and autologous SCT are included as alternative health states followed by molecular remissions following autologous SCT or allogeneic SCT. Following second-line therapy, patients reaching complete molecular remission can also undergo HSCT.

The proportion of patients in each health state over time was estimated using transition probabilities derived from the APL0406 study.[3] Modelled efficacy outcomes are outlined in the table below and include haematological complete remission rate (first line), molecular remission rate after first line, and probability of relapse (at 24 and 48 months) for patients in first remission.

A key model assumption is that the probability of relapse remains constant after 48 months.

Table 2: Key modelled efficacy parameters

Outcome	Arsenic trioxide +tretinoin	Idarubicin +tretinoin
Haematological complete remission rate (first line)	98.45%	96.35%
Molecular remission rate after first line	100%	98.32%
Probability of relapse at 24 months for patients in first remission	0.009	0.082
Probability of relapse at 48 months for patients in first remission	0.019	0.139

Utility values used in the model for each of the 14 health states were taken from a number of published studies.[9-14] Values for key health states including first molecular remission, were based on studies where patients had chronic lymphocytic leukaemia and were adjusted to reflect patients in the pivotal study. Quality of life data were collected in the study APL0406 using the QLQ-C30 instrument, however the company states that it was not possible to access these data and map to EQ-5D values. Disutilities associated with adverse events were included.[11, 15-19]

Medicine acquisition costs, administration costs and monitoring costs were included for both treatments and were estimated for the induction and consolidation phases. The acquisition costs were based on a patient weight of 75.9kg (the average weight of patients within study APL0406). No vial sharing was assumed in the base case. The model included health state costs, which included follow up costs whilst in remission, palliative/end of life costs and allogeneic and autologous SCT costs. Administration costs were assumed to include hospitalisation (bed days), outpatient visits and IV infusion costs. Resource use was based on published literature, clinical expert opinion and assumption.[6, 20, 21] The model also included adverse event costs for both treatment arms.[2, 22-30] The probability of experiencing an adverse event was taken from the pivotal study, whilst the duration of event was based on a number of published studies.
The base case and sensitivity analyses results are included in the tables below.

Table 3: Base case results

Treatment	Incremental costs/savings	Incremental QALYs	ICER
Idarubicin plus tretinoin	-	-	-
Arsenic trioxide plus tretinoin	-£12,984	3.81	Dominant

QALY=quality-adjusted life-year, ICER=incremental cost-effectiveness ratio

Table 4: Scenario analyses results

Variable	Incremental costs	Incremental QALYs	ICER
Assuming no relapses from year 2 onwards (applies to both arms)	£23,557	2.74	£8,604
Apply the same 24 month probability of relapse (8.2% applied to both arms)	-£1,350	3.46	Dominant
Apply the same 48 month probability of relapse (6.6% applied to both arms)	£38,234	2.33	£16,375
Assumption that patients who fail first line treatment with arsenic trioxide plus tretinoin are given idarubicin plus tretinoin second line.	-£11,869	3.54	Dominant
No allogeneic transplant (probability of transitioning to this health state is 0 for both arms)	£237	3.14	£75
Combined scenario analysis which assumes the same probability of relapse at 48 months for both arms, no allogeneic transplant and that patients who fail first line treatment with arsenic trioxide plus tretinoin receive idarubicin plus tretinoin as second line.	£32,940	1.91	£17,270

QALY=quality-adjusted life-year, ICER=incremental cost-effectiveness ratio

There were a number of limitations with the analysis, these included the following;

- The company assumes that the probability of relapse remains constant over time i.e. the differential treatment effect at 48 months is assumed to continue throughout the modelled time horizon. Given the lack of long term data supporting this assumption, this may not be appropriate. However the company has provided scenario analyses which test long term relapse assumptions. Results were somewhat sensitive when the probability of relapse after 48 months is assumed to be the same in both treatment arms.
- The model allows for transitions from the second-line induction or second-line remission health states to the allogeneic SCT health state, which is subject to some uncertainty and may overestimate costs within the comparator arm. The company was asked to provide a scenario analysis whereby the probability of moving into the allogeneic SCT health state is 0 for both treatment arms. The results of this analysis are outlined in Table 4 above.
- The sensitivity analyses provided by the company shows that the base case ICER is relatively robust to changes in key parameters. However in order to determine an upper bound (conservative) ICER, the company was asked to provide a combined scenario analysis which assumes no difference in relapse rates from 48 months onwards, that patients who fail first line treatment with arsenic trioxide plus tretinoin are given idarubicin plus tretinoin second line and the probability of moving into the allogeneic SCT health state is 0 for both treatment arms. Results are provided in Table 4 above.

Despite the weaknesses outlined above, the economic case has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Leukaemia CARE and Bloodwise, which are both registered charities.

- Leukaemia CARE has received 12.6% pharmaceutical company funding in the past two years, with none from the submitting company. Bloodwise has received 0.9% pharmaceutical company funding in the past two years, with none from the submitting company.

- Acute promyelocytic leukaemia (APL) is a rare form of blood cancer. APL is a rapidly progressing condition, the majority of patients start treatment the same day as diagnosis. The urgent need to start treatment and the fact that many patients are not expecting a cancer diagnosis can mean there is little time for a patient to understand and cope with their diagnosis. Common symptoms include bruising, bleeding, fatigue and infections. The emotional, physical and financial impact of an APL diagnosis are all closely interlinked and together, contribute to APL significantly affecting the day-to-day lives of not only a patient, but their family too.

- People with APL are often treated with tretinoin alongside anthracycline-based chemotherapy. Although they can be effective in inducing remission, chemotherapy can have significant, harmful side-effects both in the short and long-term, with consequences for their ability to work and live a normal life. In a survey conducted by one of the patient groups, 56% of APL patients reported being hospitalised as a result of side effects.

- In newly diagnosed patients, arsenic trioxide (in combination with tretinoin) offers an alternative to anthracyclines, for less fit patients as there are significantly less toxicities associated with the arsenic trioxide treatment. Fewer side effects compared to chemotherapy allows some patients to continue working throughout treatment which reduces pressure on the patients and their families and carers.

It was highlighted that although there are more hospital visits required to administer arsenic trioxide, the increased likelihood of a full remission compared to current treatment regimens is of significant benefit.

Additional information: guidelines and protocols

Guidelines predate the license extension for arsenic trioxide in the first-line setting.
An international expert panel, The European LeukemiaNet (ELN), published consensus guidance on the management of APL in 2009.[31] The guideline recommends that the standard induction treatment in newly diagnosed patients with APL is with tretinoin and anthracycline-based chemotherapy. In patients with relapsed disease, it recommends that arsenic trioxide is considered the best treatment option in this setting, given its high antileukaemic efficacy in relapsed patients and its relatively favourable toxicity profile.

The European Society for Medical Oncology (ESMO) published guidance entitled Acute myeloblastic leukaemias in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up in August 2013.[5] This guideline also recommends that induction therapy with tretinoin and an anthracycline is standard first-line treatment. It notes the potential of arsenic trioxide but highlights that long-term results were awaited at that time.

The British Society for Haematology last updated its guidelines on management of acute myeloid leukaemia in adults (outside of pregnancy) in 2006; they have been archived.[2]

Additional information: comparators

Idarubicin with tretinoin.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Arsenic trioxide plus tretinoin	**Induction:** **Arsenic trioxide 0.15mg/kg/day IV plus tretinoin orally 45mg/m^2 daily until complete remission is achieved (up to 60 days)** **Consolidation:** **Arsenic trioxide 0.15mg/kg/day IV, five days per week (four weeks on and four weeks off, for a total of four cycles) plus tretinoin orally 45mg/m^2 (two weeks on, two weeks off, for seven cycles).**	**Induction: 18,672** **Consolidation: 25,242**
Idarubicin plus tretinoin	Induction:	Induction: 2,899

	Idarubicin 12mg/m^2/day IV (on days 2, 4, 6 and 8) and tretinoin orally 45mg/m^2/day until remission for a maximum of 60 days Consolidation: Three one month cycles: idarubicin IV in cycle 1 (5mg/m^2 on days 1 to 4) and cycle 3 (12mg/m^2 on day 1); mitoxantrone IV (10mg/m^2 on days 1 to 5) in cycle 2. with tretinoin orally 45mg/m^2/day on days 1 to 15 of each cycle.	Consolidation: 2,257

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 28 January 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Cost calculated using weight 70kg and body surface area 1.8m^2 and based on dosing regimens in APL0406 study. IV: intravenous

Additional information: budget impact

The company assumed that the number of patients eligible for treatment was 7 in all years. The market share was assumed to be 100% in all years. The gross impact on the medicines budget was estimated to be £767k in all years. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £412k in all years.

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This assessment is based on data submitted by the applicant company up to and including 12 April 2019.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via

the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.