Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2283

trabectedin 0.25mg and 1mg powder for concentrate for solution for infusion (Yondelis®)

Immedica

9 October 2020

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 assessed under the orphan and end of life process

trabectedin (Yondelis®) is accepted for use within NHSScotland.

Indication under review: Treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.

Trabectedin, compared with an alkylating chemotherapy, increased progression-free survival but not overall survival in patients with advanced liposarcoma or leiomyosarcoma who had previously been treated with an anthracycline-based chemotherapy.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chairman
Scottish Medicines Consortium

Indication

Treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.[1]

Dosing Information

The recommended dose is 1.5 mg/m^2 body surface area, administered as an intravenous infusion over 24 hours with a three-week interval between cycles.
Trabectedin must be administered under the supervision of a physician experienced in the use of chemotherapy. Its use should be confined to qualified oncologists or other health professionals specialised in the administration of cytotoxic agents.
Administration through a central venous line is strongly recommended and patients must be pretreated with corticosteroids for both anti-emetic and hepatoprotective effects.[1]

Product availability date

October 2007
Trabectedin meets SMC orphan and end of life criteria for this indication.

Summary of evidence on comparative efficacy

Trabectedin is an anti-cancer medicine that binds to DNA triggering a cascade of events that disturb the cell cycle. It has been shown to have anti-proliferative effects in human tumour cells.[1]

An open-label phase III study (ET743-SAR-3007) recruited patients aged at least 15 years with unresectable locally advanced liposarcoma or leiomyosarcoma who were previously treated with at least an anthracycline combined with ifosfamide or an anthracycline plus at least one other cytotoxic chemotherapy regimen. They had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1, adequate bone marrow, renal and liver function and measurable disease on Response Evaluation in Solid Tumours (RECIST) version 1.1. Patients were randomised in a 2:1 ratio to trabectedin 1.5mg/m^2 by 24-hour intravenous (IV) infusion via central line (after premedication with dexamethasone 20mg IV) or dacarbazine 1g/m^2 by 20 to 120 minute IV infusion. Study drugs were given on day 1 of a 21-day cycle and continued until disease progression or unacceptable toxicity. The primary outcome was overall survival assessed in all randomised patients.[2-4]

At the final analysis of overall survival (on 5 January 2015) there was no significant difference between the groups for overall survival. An interim analysis of overall survival (on 16 September 2013) was the final analysis of progression-free survival (PFS), defined as time from randomisation to progression assessed by investigator using RECIST version 1.1 or death from any cause. PFS was longer with trabectedin compared with dacarbazine.[2,3] Table 1 details these results and other secondary outcomes: objective response rate (ORR, defined as complete or partial response) and clinical benefit rate (CBR, defined as complete or partial response or durable stable disease for at least 18 weeks).[2,3]

Table 1: Primary and secondary outcomes of ET743-SAR-3007 study.[2,3]

		Trabectedin	Dacarbazine
Data cut-off 5.12.15			
Overall survival (primary outcome)	Events (n/N)	258/384	123/193
	Median (months)	13.73	13.14
	Hazard ratio (95% CI)	0.93 (0.75 to 1.15), p=0.49	
Data cut-off 16.9.13			
Progression-free survival	Events (n/N)	217/345	112/173
	Median (months)	4.2	1.5
	Hazard ratio (95% CI)	0.55 (0.44 to 0.70)	
	6-month rate*	37%	14%
Objective response rate	Events	9.9% (34/345)	6.9% (12/173)
	Odds ratio (95% CI)	1.47 (0.72 to 3.2)	
Clinical benefit rate	Events	34%	19%
	Odds ratio (95% CI)	2.3 (1.45 to 3.7)	

PFS = progression-free survival; CI = confidence interval; Events (n/N) = number of patients with an event / number at risk of an event; * = Kaplan-Meier estimate.

Quality of life was assessed by MD Anderson Symptom Inventory (MDASI), completed by patients prior to dosing on day one of each treatment cycle. MDASI is a 19-item self-reported questionnaire reflecting patients' experience across 13 symptoms and six measures of interference with physical and mental function. At the 16 September 2013 cut-off the baseline mean scores were low across all interference and symptoms items in both trabectedin and dacarbazine treatment groups, and were comparable for both treatment groups. At each cycle through to cycle 8 mean changes from baseline in symptoms severity and interference were not clinically meaningful for either treatment group.[5]

A phase II study (ET743-STS-201, which supported the product licence) compared the licensed 3-weekly trabectedin regimen with a weekly regimen and this showed similar PFS, overall survival and ORR to study ET743-SAR-3007.[6] Other supportive studies in the company submission included studies of trabectedin versus best supportive care in a phase II (JapicCTI-121850)[7] and a phase III (T-SAR)[8] study, and in uncontrolled studies (T-DIS, TR1US and NCT00003939)[9-11]. All studies were open-label label and recruited patients with advanced soft tissue sarcoma (ET743-STS-201 included only liposarcoma or leiomyosarcoma and JapicCTI-121850 included translocation-related sarcoma). Patients had failed on anthracycline-containing chemotherapy, except patients in TR1US and 15% of JapicCTI-121850 patients, who were unsuitable for this chemotherapy.[6-10] PFS, overall survival and ORR results for these studies are shown in Table 2 below.

PFS, overall survival and ORR are available from four reports of real-world evidence where trabectedin was given to patients with advanced soft tissue sarcoma who had failed on chemotherapy in a worldwide expanded access programme[12], a phase IV study in European centres[13] and in retrospective analyses of patients treated in France and Italy.[14,15] See Table 2.

Table 2: Progression-free survival, overall survival and objective response rate with trabectedin.[6-15]

Study	Treatment Group	N	Median PFS (months)	Median OS (months)	ORR (%)
Studies versus best supportive care or no control group					
ET743-STS-201	Trabectedin licensed dose	136	3.3	13.9	5.6
	Trabectedin weekly	134	2.3	11.8	1.6
JapicCTI-121850	Trabectedin licensed dose*	37	5.6	-	8
	Best supportive care	36	0.9	-	0
T-SAR	Trabectedin licensed dose	52	3.0	-	
	Best supportive care	51	1.4	-	
T-DIS	Trabectedin licensed dose	27	7.2	27.9	
	Trabectedin for 6 cycles	26	4.0	16.5	
TR1US	Trabectedin licensed dose	24	4	9	8
NCT00003939	Trabectedin licensed dose	104	3.4	9.2	7.7
Real-world evidence					
Worldwide	Trabectedin licensed dose	807	-	11.9	5.9
Europe	Trabectedin licensed dose	218	5.9	21.3	27
France	Trabectedin licensed dose	885	4.4	12	17
Italy	Trabectedin licensed dose‡	420	-	-	11.9

*1.2mg/m^2 used instead of 1.5mg/m^2; ‡ 1.5mg/m^2 or 1.3mg/m^2, PFS = progression-free survival; OS = overall survival; ORR = objective response rate.

The submitting company compared trabectedin with pazopanib for PFS and overall survival in a matching-adjusted indirect comparison (MAIC) in adults with advanced soft tissue sarcoma who had received previous anthracycline-based chemotherapy. This was based on data from the open-label phase III studies ET743-SAR-3007 (trabectedin versus dacarbazine)[2-4] and PALETTE (pazopanib versus placebo).[16,17] The results suggested that PFS and overall survival were similar for trabectedin and pazopanib.

Summary of evidence on comparative safety

The safety profile of trabectedin is well characterised and includes fatigue, gastro-intestinal, liver and haematological toxicity.[1]

In the ET743-SAR-3007 study adverse events within the trabectedin and dacarbazine groups were consistent with the established safety profiles of these medicines. The following adverse events were reported more frequently in the trabectedin group, compared with the dacarbazine group: nausea (73% and 49%), fatigue (67% and 51%), vomiting (44% versus 21%), constipation (36% versus 28%), decreased appetite (34% versus 20%), diarrhoea (34% versus 23%), dyspnoea (25%

versus 19%) and peripheral oedema (24% versus 14%). Trabectedin was associated with more reports of elevated alanine transaminase (45% versus 6%), aspartate transaminase (35% versus 5%) and alkaline phosphatase (20% versus 7%). Neutropenia (49% and 29%) and anaemia (39% and 29%) were more commonly reported with trabectedin, whereas thrombocytopenia was less frequently reported with trabectedin (30% and 36%).[2]

Summary of clinical effectiveness issues

Soft tissue sarcomas make up a rare and heterogeneous group of cancers.[18] After gastrointestinal stromal tumours (GIST), leiomyosarcoma and liposarcoma are the most common subtypes.[2] Treatment of GIST is not relevant to this submission. Other advanced (locally advanced or metastatic) soft tissue sarcomas are generally treated first-line with anthracycline-based chemotherapy and combination with ifosfamide may be the treatment of choice. Imatinib is standard medical therapy for dermatofibrosarcoma protuberans. After failure of anthracycline-based chemotherapy or where this treatment is unsuitable, patients may be candidates for clinical studies. The following may be options, although high-level evidence is lacking: trabectedin, pazopanib (in non-adipogenic), eribulin (in liposarcomas and leiomyosarcomas), dacarbazine plus gemcitabine or gemcitabine plus docetaxel (in doxorubicin-pre-treated), regorafenib (in doxorubicin-pretreated advanced, non-adipogenic).[18]

In the ET743-SAR-3007 phase III study the primary outcome, overall survival, was not significantly different in the trabectedin and dacarbazine groups. However, trabectedin increased PFS compared with dacarbazine by approximately 2.7 months.[2,3] This study was not assessed at the time of marketing authorisation in the EU, but the improvement in PFS was considered clinically meaningful in the US FDA review.[3]

The ET743-SAR-3007 study population included patients with liposarcoma or leiomyosarcoma, which represents a subgroup of the licensed population of soft tissues sarcomas.[2] However, liposarcoma or leiomyosarcoma are common subtypes of soft tissue sarcoma and there were data on the use of trabectedin in other subtypes of soft tissue sarcoma from supportive studies (JapicCTI-121850, T-SAR, T-DIS, TR1US and NCT00003939).[7-11] The ET743-SAR-3007 study excluded patients with ECOG performance status of 2 or greater and those with unresolved toxicity from previous therapy.[2] This may limit the application of results to patients who are less fit.

The dacarbazine regimen in ET743-SAR-3007 is different from the licensed dacarbazine regimen. Dacarbazine is licensed as part of a combination chemotherapy for advanced adult soft tissue sarcomas (except mesothelioma, Kaposi sarcoma). The recommended regimen is dacarbazine daily doses of 250mg/m^2 IV infusion daily on days 1 to 5 in combination with doxorubicin every 3 weeks (ADIC regimen).[19]

The ET743-SAR-3007 study was open-label and this may have an impact on the assessment of subjective outcomes such as adverse events and the patient-reported MDASI quality-of-life questionnaire.[2,3] There were higher rates of several adverse events in the trabectedin group,

compared with dacarbazine, including fatigue and gastrointestinal effects such as nausea, vomiting, decreased appetite, diarrhoea and constipation.[2] However, these do not appear to correspond with any between group differences in the assessment of quality-of-life on MDASI.

There is no recognised standard treatment after failure of anthracycline-based chemotherapy in this group of rare and heterogeneous cancers and there are no comparative data versus any other treatment options. In the supportive, open-label, uncontrolled studies and in real world data of trabectedin at the licensed dose, median PFS ranged from 3 months to 7.2 months and overall survival ranged from 9 months to 27.9 months. Pazopanib is licensed for use in a range of soft tissue sarcoma, including leiomyosarcoma, but not liposarcoma.[20] SMC has issued advice (820/12) that pazopanib is not accepted for use within NHSScotland for treatment of adult patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

The submission included a MAIC versus pazopanib. There were a number of limitations in the MAIC: the study selection process was poorly described, as was the description of the matching process and input data were unclear. As there was no common control group, there may be bias that has not been accounted for. There were differences between the studies in the subtypes of sarcoma, for example, the PALETTE study excluded patients with liposarcoma. Due to these limitations, the results of the MIAC are highly uncertain.

Trabectedin may provide another treatment option for patients with soft tissue sarcoma, after failure of anthracycline-based chemotherapy, or in whom this treatment is unsuitable. Clinical experts consulted by SMC indicated there is unmet need for patients with this rare and diverse group of cancers, who have a poor prognosis.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group and clinical specialist representation was held to consider the added value of trabectedin, as an end of life and orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Soft tissue sarcomas are a rare and diverse group of cancers affecting patients across a wide age range. Median life expectancy is poor and approximately 18 months at time of diagnosis of advanced disease. Patients generally maintain a good quality of life until a rapid decline in the final weeks of life. Symptoms depend on the location of the primary tumour and the presence of metastasis.
- Treatment options for advanced soft tissue sarcomas are limited. For patients whose disease does not respond to, or relapses following anthracyclines and ifosfamide, or who are unsuited to receive these agents, there are currently no routinely available treatments in NHSScotland. Without treatment disease progression is inevitable over a period of two to three months.

- Trabectedin has the potential to stabilise disease and maintain patients' quality of life for longer. Experience in clinical practice indicates that a proportion of patients may achieve disease response or have stable disease for many months, allowing them to return to a level of normality and independence in their daily lives and enjoy quality time in their communities.
- Trabectedin is administered as a 24-hour inpatient infusion on one day every three weeks. Adverse effects are generally manageable, becoming less prominent 7 to 10 days after treatment. It has a different side-effect profile from other second-line treatments which may be an advantage for some patients.

Additional Patient and Carer Involvement

We received a patient group submission from Sarcoma UK, which is a registered charity. Sarcoma UK has received 1.5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Sarcoma UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

An economic analysis was presented evaluating the cost-effectiveness of trabectedin for the treatment of advanced soft tissue sarcoma, after failure of anthracyclines or ifosfamide, or who are unsuited to receive these agents. The submitting company stated that pazopanib represents the key comparator for this submission, based on data from the Scottish Sarcoma audit.

A three-state partitioned survival model ('stable disease', 'progressed disease' and 'death') formed the basis of the cost-utility analysis, with transition into subsequent states dependent on survival analysis using PFS and overall survival (OS) estimates. Costs were modelled from the perspective of NHS Scotland and social services, and a 15-year time horizon was selected. A monthly cycle length was applied.

Clinical-effectiveness estimates, in terms of PFS and OS, were obtained from an unanchored MAIC. Adjusted survival curves for trabectedin were compared against the observed data for pazopanib, and extrapolated using a log-normal distribution for all curves in the base case, based on statistical goodness-of-fit. Three other functions were considered in scenarios: Weibull, generalized Gamma and exponential. Health state utilities were derived from a burden-of-illness study which collected EQ-5D-3L data valued according to UK preferences (stable disease = 0.77; progressive disease = 0.56), with a range of adverse event disutilities applied based on published literature.[21]

Costs included medicines acquisition for trabectedin and pazopanib, as well as administration and monitoring costs for both treatments and the cost of managing adverse events. Despite both treatments requiring treatment to progression, trabectedin treatment was assumed to be a maximum of 4 cycles (based on the median duration of treatment reported in the pivotal trial for trabectedin),[6] whilst pazopanib treatment was assumed to continue for a maximum of 5.7 cycles (based on clinical opinion received by the submitting company). Subsequent treatment costs were also included, with different subsequent treatments assumed for trabectedin and pazopanib. Of

note, the cost of palliative care was included in this estimate at a cost of £12,996 per cycle, and was assumed to be required by 25% of patients in the trabectedin cohort and 41% of patients in the pazopanib cohort.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. A simple discount is also in place for pazopanib, in the form of a simple PAS.

The base case results are shown in table 3, and scenario analyses in 4. There are concerns with the implementation of the reported methods and therefore these results may not be reliable.

Table 3: Updated base case results

	Costs	**QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**
Trabectedin	£131,062	1.13	-£15,235	0.08	Dominant
Pazopanib	£146,297	1.05			

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

Scenario analyses were presented, testing alternative parametric distributions, the use of shorter time horizons, numerous combinations of alternative discount rates, and the variation of a number of parameters by an arbitrary +/- 20%. As the scenario analyses did not cover a number of important assumptions in the submission, such as duration of treatment, additional scenarios were requested. Key scenarios are summarized in table 4.

Table 4: Selected scenario analyses

	Scenario	**Incremental cost (£)**	**Incremental QALY**	**Cost-per QALY-gained (£)**
1.	**Base-case**	-15,235	0.080	Dominant
2.	Treatment duration: equal to PFS (trabectedin: 4 cycles; pazopanib: 5.7 cycles)	-3,909	0.08	Dominant
3.	Palliative care costs: 'one-off' cost at end of life, using lower cost estimate (per-cycle cost in progressed state)	8714	0.08	£106,699
4.	Palliative care costs: cost of no treatment (end-of-life care) is set to £7,287 (Georgiou and Bardsley 2014)	565	0.08	£6,914
5.	Combined scenario (Weibull function for all PFS and OS curves; treatment duration equal to PFS; palliative care costs as one-	19,095	0.06	£340,926

	off end-of-life cost; pazopanib administration cost for first cycle only)[+]			
6.	Cost-minimisation analysis: equivalent PFS, OS and treatment duration	-21,228	N/A	N/A
7.	Cost-minimisation analysis: equivalent PFS, OS and treatment duration. Costs of subsequent treatment = 0 (i.e. equal)	14,273	N/A	N/A

[+]note that the administration costs for pazopanib were erroneously applied, with the costs of administration for all cycles applied in the first cycle. QALY = quality-adjusted life-year, PFS = progression-free survival, OS = overall survival, N/A = not applicable

The submission is subject to a number of limitations, with the key issues described below:

- The estimates of clinical effectiveness rely upon an unanchored MAIC, the methods of which were poorly reported and the results of which are highly uncertain. Although adjusting for a number of baseline covariates, the MAIC does not appear to consider the prognostic implications of subsequent treatment on overall survival. Given the level of uncertainty, it may be appropriate to assume clinical equivalence, in terms of PFS and OS, between the two treatments (Scenarios 6 and 7).
- The use of a median treatment duration underestimates the average total cost of both treatments, and results in a structural issue where duration of time in stable disease (PFS) is not linked to duration of treatment. In reality, costs of medicines acquisition and administration will continue to be incurred while patients remain on treatment with stable disease, and as such the treatment duration should correlate with progression-free survival. Alternative scenarios were requested to test the implications of this assumption, resulting in a significant increase in the total cost of trabectedin (Scenario 2).
- An administration cost of £132 has been assumed for each cycle of pazopanib treatment. This would appear to overestimate the costs associated with dispensing this oral medicine. However, sensitivity analysis was subsequently provided which showed removing this cost from the model had minimal impact on the results.
- The cost of best supportive care (palliative care) is applied on a treatment-specific basis, rather than for the proportion of patients approaching the end of their lives over time. Additionally, the source of this cost input may be overestimated relative to more recent estimates for cancer care. Use of these alternative approaches, which represent standard practice in oncology modelling, results in an increased ICER (Scenario 3).

The Committee considered the benefits of trabectedin in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as trabectedin is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted trabectedin for use in NHSScotland.

Additional information: guidelines and protocols

In 2018 the European Society for Medical Oncology (ESMO) published Soft Tissue and Visceral Sarcomas: ESMO–EURACAN Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. These note that advanced soft tissue sarcoma is treated first-line with standard chemotherapy based on anthracyclines. Multi-agent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly in subtypes sensitive to ifosfamide, when a tumour response is felt to be potentially advantageous and patient performance status is good. Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans. In general, advanced previously treated patients are candidates for clinical trials. After failure of anthracycline-based chemotherapy or the impossibility to use it, the following may be options, although high-level evidence is lacking: ifosfamide, trabectedin, pazopanib (in non-adipogenic), eribulin (in liposarcomas and leiomyosarcomas), dacarbazine plus gemcitabine or gemcitabine plus docetaxel (in doxorubicin-pre-treated), regorafenib (in doxorubicin-pretreated advanced, non-adipogenic).[18]

Additional information: comparators

Pazopanib* (in non-adipogenic), eribulin**, ifosfamide, dacarbazine plus gemcitabine or gemcitabine plus docetaxel.

*not recommended by SMC (820/12), **not recommended by SMC (2231)

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 21-day cycle (£)
Trabectedin	1.5mg/m^2 24-hour infusion on day one of 21-day cycle	3,821

Costs from BNF online on 20 May 2020. Costs calculated using the full cost of vials/ampoules assuming wastage and assuming a body surface area of 1.8m^2. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 10 patients estimated to receive treatment in year 1 and 10 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 September 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a

patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.