SMC2582

durvalumab concentrate for solution for infusion (Imfinzi®)

AstraZeneca

06 October 2023

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 full submission assessed under the end of life and orphan equivalent medicine process

durvalumab (Imfinzi®) is accepted for use within NHSScotland.

Indication under review: in combination with gemcitabine and cisplatin for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer.

In a phase III study, addition of durvalumab to current standard of care chemotherapy significantly improved overall survival and progression-free survival in adults receiving first-line treatment for advanced or metastatic biliary tract cancer.

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

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

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Durvalumab is a monoclonal antibody that blocks the interaction of programmed cell death ligand 1 (PD-L1) with programmed cell death 1 (PD-1) and CD80. It thereby enhances anti-tumour immune responses and increases T-cell activation. Durvalumab 1,500mg (or 20mg/kg, if <30kg) is given intravenously (IV) on Day 1 of 21-day cycles for eight cycles in combination with gemcitabine plus cisplatin. Then, durvalumab monotherapy is given every four weeks until disease progression or unacceptable toxicity. See Summary of product characteristics (SPC) for further information.[1]

1.2. Disease background

Biliary tract cancers (BTCs) are a heterogeneous collection of malignancies, usually adenocarcinomas, arising from the gallbladder or cystic duct or the biliary tree. There are generally no specific symptoms in the initial stages, and patients are usually diagnosed with advanced disease when curative surgery is not feasible and prognosis is poor.[2-4]

1.3. Treatment pathway and relevant comparators

The current standard of care for first-line treatment of advanced or metastatic BTC is gemcitabine plus cisplatin. This is associated with median overall survival of around 11.7 months and two-year survival rate of approximately 15%.[2-4] There is an unmet need for more effective therapies for first-line treatment of BTC.[5] In practice, durvalumab would be added to the standard first-line chemotherapy treatment for BTC, gemcitabine plus cisplatin.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Durvalumab has received an Innovation Passport allowing entry into the Medicines and Healthcare Products Regulatory Agency (MHRA) Innovative Licensing and Access Pathway (ILAP).

Eligibility for a PACE meeting

Durvalumab meets SMC end of life criteria and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The clinical evidence is from the TOPAZ-1 study detailed in Table 2.1.[2]

Table 2.1. Overview of relevant study

Criteria	TOPAZ-1 Study [2]
Study design	International, double-blind, phase III study.
Eligible patients	Adults with untreated recurrent, advanced or metastatic adenocarcinoma of the biliary tract, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma. ECOG performance status of 0 or 1 and at least one measurable lesions on RECIST v1.1.

Treatments	Durvalumab (licensed dose, see section 1.1) or placebo. All patients had eight cycles of IV gemcitabine 1,000mg/m^2 BSA and IV cisplatin 25mg/m^2 BSA on Days 1 and 8 of each 21-day cycle.
Randomisation	Stratified by disease status (initially unresectable versus recurrent) and primary tumour location (intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer). Patients equally assigned.
Primary outcome	Overall survival.
Secondary outcomes	Progression-free survival; objective response rate.
Statistical analysis	Key secondary outcome, PFS, tested if primary outcome significant. No other secondary outcomes adjusted for multiplicity or formally tested.

BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

At a planned interim analysis (data cut-off 11 August 2021), the primary outcome, overall survival, and key secondary outcome, progression-free survival (PFS), were significantly improved with durvalumab compared with placebo as detailed in Table 2.2. This was then considered the primary analysis.

Table 2.2: TOPAZ-1 study results at data cut-off 11 August 2021.[2, 6-8]

	Durvalumab	**Placebo**
	n=341	**n=344**
Median follow-up, months	16.8	15.9
Primary outcome: overall survival		
Deaths	198	226
Hazard ratio (95% confidence interval)	0.80 (0.66 to 0.97), p=0.021	
Median, months	12.8	11.5
KM estimated 2-year overall survival	25%	10%
Key secondary outcome: progression-free survival, by investigator on RECIST v1.1		
Events	276	297
Hazard ratio (95% confidence interval)	0.75 (0.63 to 0.89), p=0.001	
Median, months	7.2	5.7
KM estimated 1-year progression-free survival	16%	6.6%
Objective response rate, by investigator on RECIST v1.1 in patients with measurable disease		
Patients with measurable disease	n=341	n=343
Objective response	91 (27%)	64 (19%)
Complete response	7 (2.1%)	2 (0.6%)
Partial response	84 (25%)	62 (18%)
Odds ratio (95% confidence interval)	1.60 (1.11 to 2.31)	
Median duration of response, months	6.4	6.2

KM = Kaplan-Meier; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1. All patients received gemcitabine plus cisplatin as detailed in Table 2.1.

Additional analysis (data cut-off 25 February 2022) provide extended overall survival data, with median follow-up of 23.4 and 22.4 months in the durvalumab and placebo groups, respectively. At this cut-off, 248 and 279 patients from the respective groups had died and the following results were similar to the primary analysis: hazard ratio (HR) 0.76 (95% confidence interval [CI]: 0.64 to 0.91); median overall survival, 12.9 versus 11.3; and two-year overall survival, 24% versus 12%.[2, 6-8]

2.2. Health-related quality of life outcomes

The TOPAZ-1 study assessed health-related quality of life using the European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire (EORTC QLQ-BIL21). The addition of durvalumab to gemcitabine-cisplatin was not associated with a detriment in these outcomes or the exploratory outcome.[2, 7]

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

3. Summary of Safety Evidence

In the TOPAZ-1 study, at 11 August 2021 data cut-off, within the durvalumab and placebo groups, median (range) duration of treatment was 7.3 months (0.1 to 24.5) and 5.8 months (0.2 to 21.5). Adverse events were reported by 99% (336/338) and 99% (338/342) of patients and these were considered treatment-related in 93% and 90%, respectively. In the respective groups, grade 3 or 4 adverse events were reported by 76% and 78% of patients (treatment-related in 63% and 65%); serious adverse events were noted in 47% and 44% of patients (treatment-related in 16% and 17%); and 13% and 15% of patients discontinued therapy due to an adverse event (treatment-related in 8.9% and 11%). There were two deaths due to adverse events that were considered to be treatment-related in the durvalumab group (ischaemic stroke and hepatic failure) and one death in the placebo group (polymyositis).[2]

In the TOPAZ-1 study, at 11 August 2021 data cut-off, immune-related adverse events of special interest occurred at higher rates in the durvalumab group compared with placebo, 13% versus 4.7%, including hypothyroid events (5.9% versus 1.5%).[2]

Patients with BTC often require procedures for biliary drainage, which can be associated with cholangitis and biliary tract infections. These were more common in the durvalumab group, compared with placebo: 15% versus 8.5%. Most were high grade or serious events that required hospital admission. However, the majority of patients recovered with antibiotic treatment.[5]

Adverse events typical of chemotherapy were observed across both groups. [2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Evidence is available from a phase III randomised, double-blind, placebo-controlled study. Placebo is an appropriate comparator as durvalumab will be added to standard of care chemotherapy, gemcitabine plus cisplatin, in clinical practice.
- In patients with unresectable, locally advanced or metastatic BTC, addition of durvalumab to standard of care chemotherapy, gemcitabine plus cisplatin, significantly improved overall survival, with a median increase of about 1.5 months at the latest data cut-off (25 February 2022). PFS also significantly improved with a median increase of about 1.5 months at the first interim analysis (11 August 2021). Estimated overall survival at two years increased with durvalumab: 25% versus 10%. Quality of life measures where not substantially changed by the inclusion of durvalumab.[2, 6] A regulatory review noted that the

benefit in overall survival was modest but clinically relevant in view of the poor disease prognosis and the manageable safety profile of durvalumab.[5]

- Durvalumab is the first PD-L1 inhibitor to be licensed for first-line treatment of adults with locally advanced, unresectable or metastatic BTC.[1]

4.2. Key uncertainties

- The TOPAZ-1 study was stopped at an interim analysis (August 2021).[2] At this point, 66% (424/685) of patients had died, that is, 85% of the planned 496 deaths in the final analysis. At the latest data cut-off (25 February 2022), 77% (527/685) of patients had died (that is, more than the planned 496 deaths for the final analysis). The study is ongoing and more mature overall survival data may be available in the future, but could be confounded by subsequent therapies.[8]
- There may be a biological rationale for greater benefit with durvalumab in patients with high PD-L1 expression. However, PD-L1 status was not a stratification factor in TOPAZ-1 and post hoc interaction tests of overall survival by PD-L1 levels of 1% and 5% were not significant. There is insufficient evidence to establish PD-L1 expression as a predictive factor for response in this setting.[5]

4.3. Clinical expert input

Clinical expert input to SMC suggested that durvalumab addresses an unmet need and is a therapeutic advancement.

4.4. Service implications

Durvalumab treatment continues (every four weeks) after chemotherapy finishes. This, and resource to manage immunotherapy-associated adverse events, may have service implications, although patient numbers are expected to be low.

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

5. Patient and clinician engagement (PACE)

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

The key points expressed by the group were:

- Biliary tract cancer (BTC) is often diagnosed at an advanced and unresectable stage, where current first-line therapy with gemcitabine plus cisplatin is associated with limited overall survival of about 11.5 months. The dismal prognosis has a huge negative psychological impact on the patient and their family. They often cannot comprehend that, in contrast to other cancers, there has been no advance in first-line treatment for many years and the available therapies are very limited. There is an unmet need for more effective therapies with acceptable tolerability in this setting.

- The immunotherapy, durvalumab, increases median progression-free and overall survival

in the first-line treatment of patients with unresectable advanced BTC, with certain patients achieving benefits much greater than the average observed in the clinical study. It prolongs the limited time that patients have to spend with their family and friends. By extending the time that the disease is controlled and the patient is well, it may provide more opportunities to make memories. This may help to relieve the emotional impact of the disease, in addition to improving symptom control.

- Some patients and their family are aware of durvalumab and the benefits that the new class of immunotherapy medicines can achieve. Accessing durvalumab may provide reassurance that optimum treatment has been given and may give hope for some that improved overall survival could bridge to a time when additional therapies become available.

- Administration of durvalumab is not associated with additional hospital visits during the first eight 21-day cycles, but the visits are extended by about 1 to 1.5 hours. After this, treatment with durvalumab requires an additional hospital visit every three weeks. Patient group representatives report that patients may be happy to attend these additional visits to obtain the potential survival benefits with durvalumab. There is established clinical experience of using immunotherapies and these can be managed within routine practice.

Additional Patient and Carer Involvement

We received a patient group submission from AMMF, which is a charitable incorporated organisation. AMMF has received 32.5% pharmaceutical company funding in the past two years, including from the submitting company. A representative from AMMF participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	20 years.
Population	The submitting company requested SMC consider durvalumab for treating adults with previously untreated, locally advanced, unresectable, or metastatic BTC, including people with recurrent disease after treatment with curative intent.
Comparators	Gemcitabine plus cisplatin.
Model description	A three state partitioned survival model was used with the following health states: progression-free; progressed disease; death. The survival models for overall survival and PFS determined the proportion in each health state. Patients initially entered in the progression-free health state, receiving either durvalumab in combination with gemcitabine plus cisplatin or gemcitabine plus cisplatin. Patients in the progression-free state could transition to progressed disease or death, with patients in the progressed disease state transitioning to death. Following disease progression, patients received subsequent treatments. The cycle length of the model was one week and a half-cycle correction was applied.

Clinical data	Clinical data were from the TOPAZ-1 study.[2, 6-8] Data from the durvalumab arm were used to model outcomes for the durvalumab in combination with gemcitabine plus cisplatin patients, with data from the placebo arm used to model outcomes for those receiving gemcitabine plus cisplatin. PFS, time to treatment discontinuation (TTD) and utility values were sourced from the August 2021 data cut-off (median patient follow up of 16.8 and 15.9 months in the durvalumab and placebo arms, respectively). Overall survival, safety and subsequent treatment inputs were sourced from the February 2022 data cut-off (median patient follow up of 23.4 and 22.4 months in the durvalumab and placebo arms, respectively).
Extrapolation	To estimate long-term efficacy outcomes, overall survival and PFS data from the TOPAZ-1 study were extrapolated. Independent overall survival and PFS curves were fitted in each treatment arm. The 1-knot odds spline model was used for overall survival and PFS in the durvalumab in combination with gemcitabine plus cisplatin arm. The 1-knot normal spline model was used for overall survival and PFS in the comparator arm. The survival curves were selected based on statistical goodness of fit, visual fit to Kaplan-Meier plots, assessment of hazard functions and external (clinician or real world evidence) validation. The PFS curves were used to model the time on treatment for the intervention and comparator, with gemcitabine plus cisplatin capped at 8 cycles of treatment.
Quality of life	Utility scores were derived from EQ-5D-5L data collected from TOPAZ-1, cross-walked to EQ-5D-3L.[9] EQ-5D-5L data were collected according to separate assessment schedules, depending on whether patients were receiving treatment or had discontinued. Patients that discontinued had less frequent data collection. EQ-5D-5L data collection was stopped if a post-progressed disease patient received a non-study treatment. The mean (95% confidence interval) base case utility values were 0.797 (0.787; 0.807) for the progression-free health state and 0.679 (0.638; 0.720) for the progressed disease health state. Utility values were adjusted by age and gender.[10] Adverse event dis-utilities were applied as a one-off decrement in the first model cycle.
Costs and resource use	The model included medicine acquisition, administration, monitoring, adverse event, subsequent treatment, and end of life costs. A relative dose intensity derived from TOPAZ-1 was applied to first-line treatments to account for dosing reductions. Resource use for monitoring and disease management were sourced from clinical experts and ESMO BTC guidelines.[3]
PAS	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 discount was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. List price results were also commercial in confidence.

6.2. Results

As noted, all cost-effectiveness results were commercial in confidence and therefore cannot be presented.

The results showed that the majority of the incremental costs were from the treatment acquisition costs. Incremental QALY gain was present in both pre-progression and progressed disease health states, with the progressed disease health state generating a slightly larger incremental QALY gain.

6.3. Sensitivity analyses

The submitting company provided a range of sensitivity and scenario analysis but the results cannot be presented due to commercial in confidence issues. Table 6.2 describes the scenarios that were considered.

The largest change in the ICER was observed when considering an alternative overall survival curve for the durvalumab in combination with gemcitabine plus cisplatin arm.

Table 6.2: Scenario analyses

	Description	Base case	Scenario
1	D + Gem/Cis OS distribution	Spline odds (1 knot)	Spline normal (1 knot)
2	Gem/Cis OS distribution	Spline normal (1 knot)	Spline normal (2 knot)
3	D + Gem/Cis PFS distribution	Spline odds (1 knot)	Spline odds (3 knot)
4	Gem/Cis PFS distribution	Spline normal (1 knot)	Spline hazard (3 knot)
5	Costs and utilities	Time on treatment costs based on PFS parametric extrapolations	Time on treatment costs based on TTD parametric extrapolations
		Utility values based on progression status	Utility values based on treatment status
6	Utilities	Progressed disease utility value of 0.679	Upper bound progressed disease utility value of 0.72
			Lower bound progressed disease utility value of 0.638
7	Time horizon	20 years	5 years
			10 years

Abbreviations: D + Gem/Cis, durvalumab in combination with gemcitabine plus cisplatin; Gem/Cis, gemcitabine plus cisplatin; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation.

6.4. Key strengths

- The partitioned survival model facilitated the direct use of the time-to-event endpoints collected in the TOPAZ-1 study (overall survival and PFS), reflecting disease progression. The clinical data used in the model were relatively mature, with 73% and 81% of overall survival events recorded in the durvalumab and placebo arms respectively. PFS events were recorded in 81% and 86% of the respective arms.
- The survival analysis was conducted following NICE DSU TSD 14 and 21 guidance.[11]
- The mixed models for repeated measures approach used to derive utility values represents current best practice.

6.5. Key uncertainties

- Although the survival analysis was conducted following NICE DSU TSD 14 and 21 guidance, there were noted difficulties in the validation of the 5 year overall survival estimates for durvalumab in combination with gemcitabine plus cisplatin due to a lack of clinical experience. Furthermore, no external data were available to provide validation of the estimates. Therefore, there remains some uncertainty in the base case ICER. From the alternate plausible survival curves (that met criteria outlined in the survival curve selection process), the largest ICER increase was observed when using the 1-knot normal spline overall survival curve for durvalumab in combination with gemcitabine plus cisplatin (Scenario 1).

- The time horizon used in the analysis was a lifetime time horizon of 20 years, with less than 1% of patients alive at this time point. Based on this, the time horizon appears reasonable to capture the relevant costs and benefits of the treatment. However, given the limited long term outcome data and lack of long term clinical experience with durvalumab in combination with gemcitabine plus cisplatin, shorter time horizons may be of relevance. When considering 5 year (base case extrapolated overall survival for durvalumab in combination with gemcitabine plus cisplatin is approximately 5% at 5 years) and 10 year time horizons, the ICER increased (Scenario 7). These increases were primarily attributed to the reduction in the incremental QALY gain from the progressed disease health state, highlighting the dependence of the base case ICER on the QALYs accrued in this health state, and the potential ICER uncertainty when applying estimated long-term survival outcomes.

- The progressed disease utility value was subject to uncertainties. Firstly, there were fewer observations used to derive this compared to the progression-free health state utility value (238 observations from 173 patients compared to 4385 observations from 633 patients, respectively), as a result of the factors limiting the collection of EQ-5D-5L data for progressed disease patients. Patients that discontinued treatment as a result of progression had a maximum of 3 further EQ-5D-5L assessments, with assessments not performed if a subsequent treatment was administered. The majority of patients discontinued treatment due to progression, with nearly half the patients in each TOPAZ-1 arm receiving subsequent treatments. Furthermore, if patients progressed after discontinuing treatment pre-progression there were no EQ-5D-5L assessments following progression. Secondly, some patients continued to receive the first-line treatment following progression, potentially biasing the utility values. Finally, as EQ-5D-5L assessments were not performed upon subsequent treatment administration, the progressed disease utility value may not sufficiently capture the health related quality of life when receiving subsequent treatments. Variation in the ICER was observed when applying the 95% confidence interval for the progressed disease utility (Scenario 6). This may be sufficient to support limited uncertainty in the ICER.

- The administration costs were potentially underestimated in the economic model. The administration costs for the initial 8 cycles of durvalumab in combination with gemcitabine plus cisplatin or gemcitabine plus cisplatin should most likely be increased to reflect the longer chair time required and additional infusion days. However, when applying estimates of these higher costs the increase in the ICER was limited.

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

7. Conclusion

The Committee considered the benefits of durvalumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as durvalumab is an orphan equivalent 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 durvalumab for use in NHSScotland.

8. Guidelines and Protocols

The European Society of Medical Oncology (ESMO) Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up was published in 2022.[3]

The British Society of Gastroenterology (BSG) guidelines for the diagnosis and treatment of cholangiocarcinoma were updated in 2012.[12]

9. Additional Information

9.1. Product availability date

25 January 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
Durvalumab Gemcitabine Cisplatin	1,500mg IV on day 1 of 21-day cycles for 8 cycles then every 4 weeks 1,000mg/m^2 IV on day 1 and 8 of 21-day cycle for 8 cycles cisplatin 25mg/m^2 IV day 1 and 8 of 21-day cycle for 8 cycles	7,500 (7,398 without chemotherapy)

Costs from BNF online on 5 April 2023. Costs based on body surface area of 1.8m^2. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 142 patients eligible for treatment with durvalumab in each year to which confidential estimates of treatment uptake were applied.

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.**

References

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9. Hernandez-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. J Health Econ. 2017;55:139-52.
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This assessment is based on data submitted by the applicant company up to and including 23 June 2023.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.