Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of trabectedin for the treatment of advanced metastatic soft tissue sarcoma, in accordance with the licensed indication, based on the evidence submission from the manufacturer to NICE as part of the single technology appraisal (STA) process. The outcomes stated in the manufacturer's definition of the decision problem were overall survival (OS), progression-free survival (PFS), response rates, adverse effects of treatment, health-related quality of life, and cost per quality-adjusted life-year (QALY) gained. The clinical evidence was derived from one randomised controlled trial (RCT), in which the licensed dose of trabectedin was compared with a different dose of trabectedin, and three phase II studies. In the RCT, the median OS was 13.9 months for the licensed dose of trabectedin, which was not significantly different from that for the comparator dose of trabectedin, which was 11.8 months. From the phase II uncontrolled trials, median OS was reported as 9.2 or 12.8 months. The RCT reported significantly superior PFS for the licensed dose of trabectedin (median 3.3 months) over the comparator trabectedin dose (median 2.3 months). One phase II uncontrolled trial reported median PFS as 1.9 months in the licensed dose of trabectedin. The RCT reported PFS rates at 6 months were 35.5% for the licensed dose of trabectedin, and 27.5% for the comparator dose of trabectedin. From the phase II uncontrolled trials, PFS rates at 6 months were 24.4% or 29%. For the RCT, deaths attributed to trabectedin occurred in 3.1% of the licensed dose, and 2.3% of the comparator group. The most common severe adverse events were neutropenia,

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although with a low rate of febrile neutropenia, thrombocytopenia, and aspartate aminotransferase and alanine aminotransferase elevation, although these were reported to be non-cumulative and reversible. Following dialogue iterations with the ERG team, the manufacturer revised the model twice. However, despite revisions, errors/inconsistencies were found in the latest version of the model and were corrected by the ERG (only for the base case). In the latest manufacturer's submission, the cost per QALY gained of trabectedin compared with best supportive care (BSC) was estimated to be £56,985 for the base case using effectiveness from the STS (Soft Tissue Sarcomas)-201 trial for trabectedin and a pool analysis of the European Organisation for Research and Treatment of Cancer data set for BSC. This analysis was constrained to patients with L–sarcomas only. When the joint uncertainty between parameters was considered, the cost-effectiveness acceptability curve showed that trabectedin has a very low probability of being cost-effective at a threshold of £30,000 per QALY gained compared with BSC for any scenario. The guidance has yet to be issued by NICE.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Trabectedin for the treatment of advanced metastatic soft tissue sarcoma: a single technology appraisal'.[2]

Description of the underlying health problem

Trabectedin is licensed for patients with advanced metastatic soft tissue sarcoma having failed anthracycline and ifosfamide or for whom these agents are unsuitable.

Soft tissue sarcomas (STS) constitute a heterogeneous group of malignancies arising in soft tissues of the body including muscle, fat and blood vessels. The most frequent types are leiomyosarcoma and liposarcoma, which account for approximately 40–50% of all STS. There is an estimated annual incidence of 2000 STS in England and Wales (including gastrointestinal stromal tumour, which is excluded from this report).[3] Approximately 50% of patients present with, or develop, advanced or metastatic disease.

Scope of the evidence review group report

The principal research question was to appraise the clinical effectiveness and cost-effectiveness of trabectedin within its licensed indication for the treatment of advanced metastatic soft tissue sarcoma. Trabectedin is licensed for use in patients with advanced metastatic STS who have failed anthracycline and ifosfamide, either in combination as first-line therapy or in sequence as first- and second-line therapy. No other chemotherapies are currently licensed in the UK for STS at this point in therapy. The comparator was best supportive care. Relevant outcomes were overall survival (OS), progression-free survival (PFS), response rates (including stabilisation), adverse effects of treatment, health-related quality of life, and cost per quality-adjusted life-year (QALY) gained.

The manufacturer submitted a state transition model developed in EXCEL, with individuals followed up to 5 years (until death). The base case in the manufacturer's submission assumed that patients treated with trabectedin enter the model in the progression-free state (PFS) while patients in the best supportive care (BSC) arm enter the model in the progressive disease (PD) state. The base case was limited to patients with leukaemia (L)-sarcomas. Additional analyses requested by the ERG adjust the base case to account for differences in the starting health state. In addition, the manufacturer presented three additional scenarios. The first scenario used the pooled effectiveness of trabectedin from three

uncontrolled phase II studies which was not limited to patients with L-sarcomas. In the second and third scenarios, the manufacturer assumed that a proportion of patients in BSC would receive further chemotherapies (either 33% or 100% of patients).

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The ERG repeated, although could not replicate exactly, the searches undertaken by the manufacturer. The ERG does not believe that any relevant clinical or cost-effectiveness studies have been missed.

Following dialogue iterations with the ERG team, the manufacturer revised the model twice. However, despite revisions, errors/inconsistencies were found in the latest version of the model and were corrected by the ERG (only for the base case). These errors were identified by a review of the model structure and internal logic and the responsiveness of the results to changes in parameters values.

Results

Summary of submitted clinical evidence

Owing to the lack of any comparative trials comparing trabectedin and BSC, the main evidence in the manufacturer's submission was derived from one phase II randomised trial, in which the licensed dose of trabectedin was compared with a different dose of trabectedin. In the randomised controlled trial (RCT), median OS was 13.9 months [95% confidence interval (CI) 12.5 to 18.6] for the licensed dose of trabectedin (24-hour regimen every 3 weeks), which was not significantly different ($p = 0.1985$) from that for the comparator dose of trabectedin (weekly 3-hour regimen) which was 11.8 months (95% CI 9.9 to 14.9). From the phase II uncontrolled trials, median OS was reported as 9.2[4] or 12.8 months.[5] Historical control data, presented by the manufacturer's submission as equivalent to BSC, had median OS of 5.9–6.6 months.[6] The RCT reported significantly ($p = 0.04$) superior PFS for the licensed dose of trabectedin (median 3.3 months) over the comparator trabectedin dose (median 2.3 months). One phase II uncontrolled trial reported median PFS as 1.9 months in the licensed dose of trabectedin.[5] The RCT reported PFS rates at 6 months were 35.5% (95% CI 27.1 to 43.9) for the licensed dose of trabectedin, and 27.5% (95% CI 19.4 to 35.5) for the comparator dose of trabectedin. From the phase II uncontrolled trials, PFS rates at 6 months were 24.4%[7] or 29%.[4] Historical control data, presented by the manufacturer's submission as equivalent to BSC, reported PFS rates at 6 months of 14% for patients treated with ifosfamide or dacarbazine after failure of anthracycline or 8% for patients from pooled studies on 'inactive' regimens.

For the RCT, deaths attributed to trabectedin occurred in 3.1% of the licensed dose, and 2.3% of the comparator group. Safety data for the licensed dose of trabectedin from the included RCT and three phase II studies' reported rates of grade 3/4 haematological events varied: neutropenia 34–61%; febrile neutropenia 0.8–7.0%; thrombocytopenia 12–19%; and anaemia 8–22%. Across the four included studies, rates of grade 3/4 non-haematological events varied: aspartate aminotransferase (AST) elevation 26–48%; alanine aminotransferase (ALT) elevation 20–57%; nausea 4–7%; vomiting 2–9%; and asthenia/fatigue 0–15%.

Summary of submitted cost-effectiveness evidence

In the latest manufacturer's submission, the cost per QALY gained of trabectedin compared with BSC was estimated to be £56,985 for the base case using effectiveness from the STS-201 trial for trabectedin and a pool analysis of the European Organisation for Research and Treatment of Cancer data set for BSC. This analysis was constrained to patients with L-sarcomas only.

The ERG was concerned that patients in the trabectedin arm began in a different health state than those in the BSC arm, and that those on trabectedin were assumed to have a higher starting utility. An exploratory analysis by the manufacturers in amending this assumption raised the cost per QALY gained for trabectedin compared with BSC to £61,064.

In addition to the base case, the manufacturer presented three additional scenarios. The first used the pooled effectiveness of trabectedin from three uncontrolled phase II studies which was not limited to patients with L-sarcomas; this produced

a cost per QALY gained of £50,017. In the second and third scenarios, the manufacturer assumed that a proportion of patients in BSC would receive further chemotherapies (either 33% or 100% of patients). The cost per QALY gained for these two scenarios was estimated to be £62,044 and £80,279 respectively. None of these three scenarios amended the model to take into consideration the different starting utilities between the trabectedin and BSC arms.

When the joint uncertainty between parameters was considered, the cost-effectiveness acceptability curve showed that trabectedin has a very low probability of being cost-effective at a threshold of £30,000 per QALY gained compared with BSC for any scenario.

Commentary on the robustness of submitted evidence

Limited data were available. The main evidence in the manufacturer's submission was derived from one phase II randomised trial, in which the licensed dose of trabectedin was compared with a different dose of trabectedin. The population in this trial was limited to L-sarcomas. Supplementary data were presented from three uncontrolled phase II trials of the licensed dose of trabectedin. Owing to the lack of a relevant comparator group in the included trabectedin trials, the manufacturer's submission reported data from a database of other studies that are suggested to equate to BSC. The manufacturer acknowledged there were limitations with these controls, which, in addition to being historical comparisons, were from studies with populations comprising types of STS not restricted to L-sarcomas, and Eastern Cooperative Oncology Group (ECOG) performance status not confined to 0–1. This would bias against these controls for effectiveness data. There were some data available for ifosfamide studies restricted to a population similar to the trabectedin trials. Data presented in the clinical effectiveness section did not have OS calculated appropriately in all cases, and for OS and PFS data, further chemotherapy was given to some patients, thus making treatment not just BSC.

Iterations were needed to amend errors found by the ERG, which included errors in the treatment cost and additional analyses to explore the likely impact of the different starting health states. The ERG, however, still had concerns regarding the structure of the model and its ability to capture the cost-effectiveness of trabectedin for adults with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide. Firstly, the ERG had concerns about the potential non-comparability between patients included in studies to derive the effectiveness for trabectedin and BSC despite the adjustment of the Weibull curves for age, gender, histopathology and World Health Organization performance score. Secondly, the base case focuses on patients with L-sarcomas only and may not be generalisable to patients with other forms of STS. Thirdly, despite the attempt to adjust for the differences in the starting health state, uncertainties still exist on the likely impact of such model structure. Fourthly, while no utility values are available for patients with STS, there are uncertainties about the appropriateness of using utility values for patients with lung cancer as a proxy for STS. Fifthly, the probabilistic sensitivity analyses did not capture all the uncertainty within the decision, for example, the model assumed no correlation between time to disease progression and OS, nor correlation between the utility estimates for health states or the number of 1-mg and 0.25-mg vials used. Finally, the proportion of patients treated did not vary according to the proportion of patients in PFS. It is unclear how incorporating these correlations would change the mean cost per QALY, although it is likely that the range in the results generated from the PSA would increase.

Conclusions

Although the ERG does not believe relevant studies of trabectedin have been missed, the manufacturer's submission contained only one phase II RCT comparing trabectedin at the licensed dose compared with trabectedin at a lower dose, with population L-sarcoma patients with ECOG performance status of 0–1. Further evidence was presented from phase II uncontrolled trials of trabectedin. Data for BSC were taken from historical controls from a database of other studies. The manufacturer acknowledges that there are limitations with these controls. There was a rate of deaths due to toxicity of 3.1% for the licensed dose of trabectedin in the RCT. The most common severe adverse events were neutropenia, although with a low rate of febrile neutropenia, thrombocytopenia, and AST and ALT elevation, although these were reported to be non-cumulative and reversible.

Despite iterations with the ERG, the ability of the model to capture the cost-effectiveness of trabectedin for adults with advanced STS after

failure of anthracyclines and ifosfamide is unclear. Uncertainties exist about the potential non-comparability between patients in the trabectedin and BSC arm, the likely impact of the differences in the starting health state and the use of utility values for lung cancer as a proxy for STS patients. It is also unclear how results for the base case would be generalisable to patients with other forms of STS.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance issued by NICE in February 2010[8] states that:

Trabectedin is recommended as a treatment option for people with advanced soft tissue sarcoma if: treatment with anthracyclines and ifosfamide has failed, or they are intolerant of **or** have contraindications for treatment with anthracyclines and ifosfamide; **and** the acquisition cost of trabectedin for treatment needed after the fifth cycle is met by the manufacturer. This last clause reflects the patient access scheme submitted by the manufacturer, with the manufacturer offering the acquisition cost of the drug after the fifth cycle, this led to a considerable reduction of the ICER, from £61,000 to about £34,000.

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