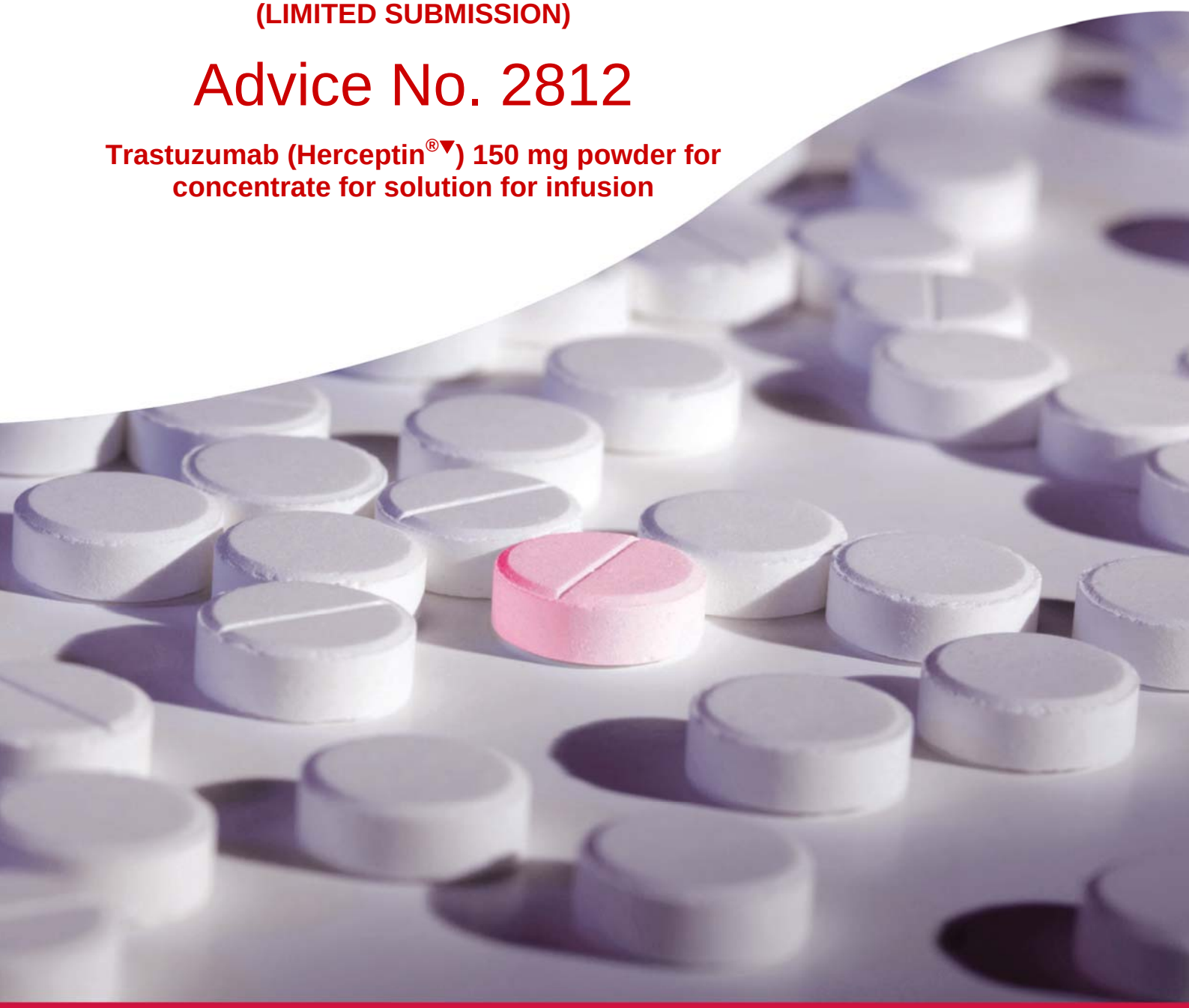
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 2812

Trastuzumab (Herceptin®▼) 150 mg powder for concentrate for solution for infusion



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 2812
Trastuzumab (Herceptin®▼) 150 mg powder for concentrate for solution for infusion

This assessment report is based on evidence from a limited submission by Roche Products Ltd on 23 March 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Trastuzumab (Herceptin®▼) is indicated for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. This submission covers the licence extension for treatment with trastuzumab in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. Please see the Summary of Product Characteristics (SPC) for licensed indications not covered by this submission[2].
Marketing authorisation date	19 December 2011[3].
Comparator(s)	Neoadjuvant chemotherapy and surgery with sequential adjuvant trastuzumab.
Limited submission details	The licence extension under consideration allows treatment with trastuzumab in combination with neoadjuvant chemotherapy for HER2-positive early breast cancer. This means that for eligible patients, trastuzumab may be initiated at the same time as neoadjuvant chemotherapy, rather than post-surgery. There is no change in the dose or treatment duration of trastuzumab from current practice (administration of trastuzumab following surgery); therefore, there is no additional budget impact anticipated. Trastuzumab for the above indication met the following criteria for a limited submission: • A minor licence extension. • Anticipated minimal budgetary impact in NHS Wales. • Estimated small difference in cost compared to comparator.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence provided

The company submission did not include a comparison of the licence extension under consideration and the comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC). The company described results from the NOAH study; an open-label, randomised, controlled, phase III superiority trial of trastuzumab alongside neoadjuvant chemotherapy followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone (i.e. no trastuzumab) in patients with HER2-positive locally advanced or inflammatory breast cancer[1,4]. In this study, trastuzumab was administered as an 8 mg/kg loading dose followed by ten cycles of 6 mg/kg every three weeks alongside neoadjuvant chemotherapy, or every four weeks if treatment included

cyclophosphamide, methotrexate or fluorouracil. After surgery, additional cycles of trastuzumab were given, starting before or during radiotherapy, to complete one year of trastuzumab treatment. At three-year follow-up, trastuzumab significantly improved event-free survival (EFS; defined as recurrence, progression or death) in patients with HER2-positive early breast cancer (n = 235): EFS was 71% for patients that received trastuzumab (95% confidence interval [CI]: 61–78%; 36 events) versus 56% for those that did not (95% CI: 46–65%; 51 events) with an unadjusted hazard ratio of 0·59 (95% CI: 0·38–0·90; p = 0·013). Overall survival at three years, based on Kaplan-Meier estimates, was increased in the trastuzumab arm (87%, compared with 79% for neoadjuvant chemotherapy alone), but the difference in the number of deaths was not significant between the two groups[4].

Following positive results of adjuvant trastuzumab trials, HER2-positive patients in the neoadjuvant chemotherapy alone group were offered one year of adjuvant trastuzumab post-surgery. Nineteen patients crossed over to adjuvant trastuzumab[4]; of these, five patients experienced an EFS event after cross-over[5]. In a sensitivity analysis, where data were censored at the time of their first trastuzumab infusion, the reduction in risk of an EFS event was calculated as 41% (unadjusted hazard ratio 0.59; 95% CI: 0.40–0.88; p = 0.0084)[5].

Adverse events (AEs) were similar between the groups: grade 3/4 AEs were balanced, as were cardiac events; however, two patients receiving trastuzumab (2%) developed symptomatic cardiac failure which was responsive to treatment. Trastuzumab was discontinued before one year in eight (7%) patients[4]. No unexpected new safety signals were observed in either arm[5].

2.2 Points to note

- The company submission did not include a comparison of the licence extension under consideration (trastuzumab in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab) with the comparator requested by AWTTC (neoadjuvant chemotherapy, surgery and sequential adjuvant trastuzumab). The company highlighted that at the time of trial design trastuzumab was not the standard of care. Gianni et al accept that, as a result, they cannot conclude that the neoadjuvant and adjuvant administration of trastuzumab led to improvement in EFS over adjuvant administration of trastuzumab alone[4].
- The NOAH study highlighted improvements in pathological complete response, which Gianni et al suggest may confer other advantages, such as improving rates of breast conserving therapy in patients eligible for surgery[4].
- The Committee for Medicinal Products for Human Use (CHMP) reported results from the NOAH study at a median follow-up of 3.8 years for the trastuzumab-receiving arm; CHMP concluded that key efficacy and safety results at this point were very similar to the published data, which related to a median follow up of 3.2 years[4,5].
- CHMP noted that the chemotherapy regimen used in the NOAH trial reflects ten-year-old practice; taxane- and anthracycline-containing chemotherapies are now considered standard treatment in the adjuvant and neoadjuvant setting. However, they acknowledged that supportive studies provided by the applicant company employed regimens that are in line with current guidelines and showed efficacy regarding pathological complete response[5].
- Gianni et al suggest that the crossing over of patients to the trastuzumab arm may have prevented the observation of a significant difference in overall survival[4].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company estimates that there are approximately 40 HER2-positive early breast cancer patients in Wales who would be eligible to receive trastuzumab in the neoadjuvant setting (company data on file)[1]. The company-reported cost of trastuzumab when administered following neoadjuvant chemotherapy and surgery is £20,913 per patient per year (assuming a 70 kg patient and no vial wastage). Following the license extension under consideration in this submission, trastuzumab would be initiated pre-surgery, alongside neoadjuvant chemotherapy, rather than post-surgery. In this case, the number of doses would remain unchanged; however, as these would be given alongside chemotherapy, this could reduce the total number of hospital attendances, which the company suggests will reduce the economic burden of administration and would allow early treatment completion for eligible patients. Therefore, the company concludes that there will be no additional costs to NHS Wales associated with the license extension under consideration[1].

3.1.1 AWTTC critique of the budget impact analysis

There is uncertainty surrounding the number of patients that would be eligible for treatment with trastuzumab in combination with neoadjuvant chemotherapy, as this is based on company data on file and has not been verified. The annual cost of trastuzumab assumes vial sharing; however, irrespective of whether vial sharing or vial wastage occurs, assuming that trastuzumab will now be delivered alongside neoadjuvant chemotherapy, in the same number of doses as currently administered, it is reasonable to conclude that no additional costs for NHS Wales would be expected.

3.2 Comparative unit costs

Table 1 shows examples of trastuzumab acquisition costs for the treatment of a 75 kg patient with HER2-positive early breast cancer (requiring a dose using whole vials). Note that the same acquisition costs would apply to the delivery of trastuzumab in both adjuvant and neoadjuvant followed by adjuvant settings. These estimates do not take into account administration costs, which could be greater for the once-weekly regimen compared with the three-weekly regimen.

Table 1. Examples of trastuzumab acquisition costs for the treatment of HER2-positive early breast cancer

Drug	Licensed regimens[2]	Annual cost per 75 kg patient
Trastuzumab (Herceptin®▼) 150 mg powder in vial	1. Loading dose of 8 mg/kg followed by maintenance dose of 6 mg/kg every three weeks beginning three weeks after the loading dose	£21,592
	2. Loading dose of 4 mg/kg followed by maintenance dose of 2 mg/kg every week	
Costs are based on MIMS list prices[6].		

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, trastuzumab is appropriate for specialist only prescribing within NHS Wales for the stated indication.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 24 April 2012
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Roche Products Ltd. Form C: limited appraisal submission. Trastuzumab (Herceptin®▼). Mar 2012.

2 Roche Products Ltd. Herceptin®▼. Summary of Product Characteristics. Feb 2012. Available at: http://www.medicines.org.uk/EMC/medicine/3567/SPC/Herceptin+150mg+Powder+for+concentrate+for+solution+for+infusion/. Accessed May 2012.

3 European Medicines Agency. Herceptin®▼. Procedural steps taken and scientific information after the authorisation. May 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000278/WC500049820.pdf. Accessed May 2012.

4 Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *The Lancet* 2010; 375 (9712): 377-84.

5 European Medicines Agency. Assessment report for trastuzumab (Herceptin®▼). Procedure No.: EMEA/H/C/000278/II/57. 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000278/WC500126896.pdf. Accessed May 2012.

6 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2012. Available at: http://www.mims.co.uk/. Accessed May 2012.