National Essential Medicine List Review Process
Component: Oncology

Medication names: Trastuzumab

Date of review: 24 February 2016

Indication: Adjuvant treatment for early stage HER-2 positive breast cancer

Introduction:

Breast cancer remains the most commonly diagnosed cancer in South Africa (18 - 21% of all cancers), with an estimated 6 000 new cases of females diagnosed histologically in 2010.[1] Globocan reported the mortality due to breast cancer in females in 2012 as 3 848.[2]

A limited list of oncology medicines was introduced on the National Essential Medicines List (EML) in 1998. Medicine treatment for breast cancer has since been expanded to 7 medicines, excluding hormonal therapy. (Refer to Annexure A for the current care package for the management of breast cancer on the Essential Medicines List.)

For women diagnosed with early-stage invasive breast cancer, the standard of care was curative surgery, with or without radiotherapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of randomised clinical trials with a 15-year follow-up established the efficacy of adjuvant chemotherapy, with anthracycline-based regimens demonstrating superiority.[3] However, even with optimal adjuvant therapy, a significant number of women develop recurrent disease.

Increased levels of human epidermal growth factor receptor 2 (HER2) on cell surfaces is caused by the amplification of the HER2 gene or over expression of the HER2 protein. This leads to an increase in intracellular tyrosine kinase activity and activation of signal transduction pathways. This in turn causes inhibition of apoptosis and promotion of cell growth, cell division, angiogenesis and metastasis.[4]

HER2 protein over expression or gene amplification has been reported to occur in approximately 20% of all breast cancers.[5] HER2/neu positive breast cancer is very aggressive and has a high frequency of recurrence, shortened disease free survival (DFS) and overall survival (OS), compared to patients whose tumours do not over express HER2.

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody specifically targeting the extracellular domain of HER2.[4] As a result, trastuzumab has been shown to inhibit the proliferation of human tumour cells that over express HER2.

The system for the selection of essential medicines considers clinical need, evidence of efficacy, quality, safety, affordability and implications for practice. Selection of an essential medicine begins with a review of the best available evidence and, if it is found to be clinically suitable, it is subjected to an economic analysis to determine affordability. This health technology assessment examines the clinical effectiveness, safety and cost of trastuzumab for consideration for inclusion on the National Essential Medicines List (EML).

Search strategy and selection of studies:
Electronic literature surveys evaluating the effectiveness and safety of trastuzumab using the following terminology were performed:

PubMed Database:
"trastuzumab"[MeSH Terms] OR herceptin[Text Word] AND "antibodies, monoclonal"[MeSH Terms] OR monoclonal antibodies[Text Word] AND "Antineoplastic Agents"[Mesh] AND "Breast Neoplasms"[Mesh] AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]) AND (("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) AND ("humans"[MeSH Terms] OR "humans"[All Fields]) AND English[All Fields]) AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]) AND ("2011/01/01"[PDAT] : "2016/12/31"[PDAT])

This returned 44 studies. Of these, 39 were excluded based on the following:

- The studies did not review trastuzumab (15);
- Efficacy or safety was not investigated (6);
- The comparator was not chemotherapy or the intervention was a combination of trastuzumab plus other (13);
- The studies were sub-analyses of a pivotal trial (5).

The remaining five trials were included for analysis.[6-10] Review of reference lists elicited further studies for inclusion.

Further investigation elicited 3 more recent meta-analyses: a Cochrane review from 2012[11], a meta-analysis investigating a subset of patients with tumours $\leq$ 2 cm[25], and one comparing the benefits of sequential *versus* concurrent trastuzumab therapy.[24]

An electronic search for health technology assessments and meta-analyses of trastuzumab was conducted using Google Scholar, yielding four additional studies.[12-15]

Evidence synthesis and quality:

A summary of the evidence evaluating the effectiveness of trastuzumab for DFS and OS is outlined in Tables 1 and 2 below. Refer to Annexures B and C for a more detailed description of trials evaluating the efficacy and safety of adjuvant trastuzumab for the treatment of early-stage breast cancer.

Efficacy **(refer to Tables 1-2):**

Table 1: Effectiveness: Disease-free survival (Summary of Annexure B)

Ref.	Trial	Follow-up (months)	N followed up		Disease free survival		HR (95% CI)	ARR	NNT
			Trastuzumab	Observation	Trastuzumab	Observation			
16	HERA	12	1694	1693	127	220	0.54 (0.43-0.67)	5.5%	19
10	HERA 4yr follow up	48.4	1703	1698	369	458	0.76 (0.66-0.87)	5.3%	19
7	HERA 8yr follow up	48.4	1703	1698	471	570	0.76 (0.67 - 0.86)	5.9%	18
17	FinHER interim	37	115	116	12	27	0.42 (0.21 to 0.83)	9%	11
18	FinHer final	62	115	116	22	31	0.65 (0.38 to 1.12)	7.6%	13
8	PHARE	42.5	1690	1690	175	219	1.28 (1.05 to 1.56)	2.6%	39
19	NSABP B31	24	1672	1679	133	261	0.48 (0.39 to 0.59)	7.6%	14
20	NSABP B31 4yr follow up	46.8	2028	2017	290	489	0.52 (0.45 to 0.6)	9.9%	11
21	NSABP B31 8yr follow up	100	2028	2018	286	418	0.63 (0.54-0.73)	6.6%	16
9	Sequential vs. concurrent trastuzumab	72	1087	1097	165	225	0.69 (0.57 to 0.85)	8.3%	12

HR - hazard ratio; LVEF - left ventricular ejection fraction; CI - confidence interval; ARR - absolute risk reduction; NNT - number needed to treat

Table 2: Effectiveness: Overall survival (Summary of Annexure B)

Ref.	Trial	Follow-up (months)	N followed up		Overall survival		HR (95% CI)	ARR	NNT
			Trastuzumab	Observation	Trastuzumab	Observation			
16	HERA	12	1694	1693	29	27	0.76 (0.47 to 1.23)	0.47%	213
10	HERA 4yr follow up	48.4	1703	1698	182	213	0.85 (0.70 to 1.04)	1.9%	54
7	HERA 8yr follow up	48.4	1703	1698	278	350	0.76 (0.65 to 0.88)	4.3%	24
17	FinHER interim	37	115	116	6	14	0.41 (0.16 to 1.08)	7.0%	14
18	FinHer final	62	115	116	24	42	0.55 (0.27 to 1.11)	15.3%	7
8	PHARE	42.5	1690	1690	66	93	1.46 (1.06 to 2.01)	1.6%	63
19	NSABP B31	24	1672	1679	62	92	0.67 (0.48 to 0.93)	0.018	57
20	NSABP B31 4yr follow up	46.8	2028	2017	146	228	0.61 (0.50 to 0.75)	4.1%	25
21	NSABP B31 8yr follow up	100	2028	2018	286	418	0.63 (0.54 to 0.73)	6.6%	16
9	Sequential vs. concurrent trastuzumab	72	1087	1097	96	108	0.67 (0.54 to 0.81)	1%	99

HR – hazard ratio; LVEF - left ventricular ejection fraction; CI - confidence interval; ARR - absolute risk reduction; NNT - number needed to treat

Other studies:
A meta-analysis that evaluated adjuvant chemotherapy with (concurrent or sequential) or without the administration of trastuzumab found a statistically significant increase in DFS (as primary outcome) in favour of trastuzumab combined with adjuvant chemotherapy as compared to chemotherapy alone (Odds Ratio (OR) 0.69; 95% CI 0.59-0.80; ARR 5.8%; NNT 17[*]).[24] There was also a statistically significant improvement in OS (as a secondary outcome) with trastuzumab-containing chemotherapy (OR 0.78; 95% CI 0.69-0.88; ARR 4.17%, NNT 24.). Of the 6 studies included in the review, 4 have been described in Tables 1 and 2 (see references 7, 9, 10, 16-21).

A Cochrane review comparing the safety and efficacy of trastuzumab, given with or after standard chemotherapy, found a statistically significant improvement in overall DFS in the trastuzumab group (Hazard Ratio (HR) 0.60; 95% CI 0.50-0.71). DFS was statistically significantly improved when trastuzumab was given for less than 6 months (HR 0.31; 95% CI 0.10-0.96) or for longer than 6 months (HR 0.62; 95% CI 0.52-0.72). DFS was also statistically significantly improved in the trastuzumab group when given either sequentially (HR 0.71; 95% CI 0.53-0.95) or concurrently (HR 0.54; 95% CI 0.44-0.67)[11].

For OS, there was a statistically significant improvement in trastuzumab-containing regimens over non-trastuzumab control groups (HR 0.66, 95% CI 0.57-0.77).[11] Trastuzumab-containing regimens were more effective when given for a longer period, i.e. more than 6 months (HR 0.67, 95% CI 0.57-0.89), while treatment with trastuzumab for less than 6 months failed to reach statistical significance (HR 0.55, 95% CI 0.27-1.11). OS stratified by concurrent or sequential administration of trastuzumab showed statistically significant improvement in the OS in trastuzumab-containing regimens when given concurrently (HR 0.64, 95% CI 0.53-0.76), while given sequentially (after chemotherapy) failed to reach statistical significance (HR 0.85, 95% CI 0.43-1.67).

In the Cochrane review, the results are only presented as hazard ratios (the number of events per group are not available, hence calculation of the NNT from HR may be misleading).[26]

Of the 8 studies included for analysis by Cochrane, 4 have been described in Tables 1 and 2 (refer to references 7, 10, 16-21).

[*] Assuming a Patient's Expected Event Rate of 23% for DFS[16]

A recent meta-analysis compared adjuvant trastuzumab *versus* no trastuzumab in a sub-set of HER2 positive patients with either hormone receptor (HR)-positive or HR-negative disease, together with tumours ≤ 2 cm[25]. In HR-positive disease, an absolute gain in DFS at 8 years of 7.0% (95% CI 2.7%-11.3%) in the trastuzumab group (HR 0.70, 95% CI 0.59=0.85), and an absolute gain in OS at 8 years of 3.8% (95% CI 0.5%-7.1%) was seen in the trastuzumab group (HR 0.68, 95% CI 0.52-0.89). In HR-negative disease, an absolute gain in DFS at 8 years of 9.4% (95% CI 3.9%-14.9%) was seen in the trastuzumab group (HR 0.66, 95% CI 0.49-0.88), and an absolute gain in OS at years of 8.8% (95% CI 4.5%-13.1%) was seen in the trastuzumab group (HR 0.59, 95% CI 0.0.47-0.74). Of the 5 studies included in the analysis, 4 have been described in Tables 1 and 2 (refer to references 7, 10, 16-21).

Comment:
The clinical evidence presented demonstrates that adjuvant trastuzumab improves DFS and OS outcomes compared to no trastuzumab. DFS did not significantly differ when trastuzumab was given for less than or more than 6 months[8,11] however, a longer treatment period (i.e. more than 6 months) was superior for OS compared with a shorter treatment period (i.e. less than 6 months). Treatment with trastuzumab for longer than 1 year (e.g. 2 years) did not offer additional DFS benefit to 1 year treatment[7,10-11,16]. Overall DFS was improved when trastuzumab was administered either concurrently or sequentially[11,24]. Overall improvement in OS was found with concurrent administration of trastuzumab, but not with sequential therapy[9,11,24].

Safety **(refer to Tables 3-6):**

Table 3: Summary of cardiac end points for safety analysis populations: HERA[22] (Summary of Annexure C)

End point	Observation (n=1744) N (%)	1 year T (n=1682) N (%)	1 year T vs. Observation: Difference % (95% CI)	2 years T (n=1673) N (%)	2 years T vs. Observation: Difference % (95% CI)	2 years of T vs. 1 year: Difference % (95% CI)
Cardiac death	2 (0.1)	0	-0.1 (-0.3 to 0.0)	3 (0.2)	0.1 (-0.2 to 0.3)	-
Severe CHF	0	14 (0.8)	0.8 (0.4 to 1.3)	13 (0.8)	0.8 (0.4 to 1.2)	-
Confirmed significant LVEF decrease	15 (0.9)	69 (4.1)	3.2 (2.2 to 4.3) (ARR=3.2%; NNH=30)	120 (7.2)	6.3 (5.0 to 7.6) (ARR=6.3%; NNH=15)	3.1 (1.5 to 4.6) P<0.001

LVEF - left ventricular ejection fraction; CI - confidence interval; ARR - absolute risk reduction; NNH - number needed to harm; T - trastuzumab

Table 4: Summary of cardiac end points for safety analysis population: FINHER[18] (Summary of Annexure C)

End point	Trastuzumab (N=115)		Observation (N=116)		P-value
	N	%	N	%	
LVEF decrease > 20% from baseline	7	6.8	10	10.5	0.35
Symptomatic heart failure	1	0.9	2	1.7	

LVEF - left ventricular ejection fraction

Table 5: Summary of cardiac end points in the comparison of 6 *versus* 12 months trastuzumab: PHARE[8] (Summary of Annexure C)

Adverse event	Trastuzumab 6 months (N=1690)		Trastuzumab 12 months (N=1690)		P-value
	N	%	N	%	
Treatment stopped due to cardiac events*/LVEF	32	1.9	103	6.1	
Cardiac events*	32	1.9	96	5.7	<0.0001
LVEF < 50%	79	4.7	106	6.3	0.04

LVEF - left ventricular ejection fraction; * not specified

Table 6: Summary of cardiac events in the N9831 + B-31 trials[19, 21] (Summary of Annexure C)

Cardiac event	Trastuzumab	Observation	Comment
CHF at 3 years[19]:			
- B31 part	4.1%	0.8%	Increase of 3.3% in trastuzumab group
- N9831 part	2.9%	0%	Increase of 2.9% in trastuzumab group
Death due to cardiac causes[21]	0.1% (n=3)	0.4% (n=9)	

CHF - chronic heart failure

Other studies:

The meta-analysis that evaluated adjuvant chemotherapy with (concurrent or sequential) or without the administration of trastuzumab found a higher incidence of central nervous system (CNS) recurrence (concurrent: OR 2.24, 95% CI 1.21-4.14; sequential: OR 1.25, 95% CI 0.77-2.03) than in sequential treatment.[24] The authors reported that the increased CNS incidence in the trastuzumab group could be due to increased survival. No mention was made with regards to cardiotoxicity in this meta-analysis.

In the safety analysis of the Cochrane review, an overall higher risk of CHF was found with trastuzumab (RR 5.11; 90% CI 3.00-8.72).[11] This risk was significantly higher when trastuzumab was given for more than 6 months (RR 5.39; 90% CI 3.56-8.17), whereas a

shorter treatment duration did not appear to increase the risk of CHF (RR 0.50; 90% CI 0.07-3.74). The risk of CHF was high whether trastuzumab was given sequentially (RR 11.05; 90% CI 3.46-35.29) or concurrently (RR 3.90; 90% CI 2.42-6.28).

There was also a statistically significant increase in LVEF decline in trastuzumab groups (RR 1.83; 90% CI 1.36-.47), with prolonged administration of trastuzumab showing increased risk of LVEF decline (RR 2.14; 90% CI 1.58-2.89), and no significant risk in LVEF decline in shorter treatment durations (RR 0.89; 90% CI 0.51-1.57).[11] The only trial that compared sequential and concurrent trastuzumab therapy did not observe a difference in the risk of LVEF decline (RR 0.95; 90% CI 0.60-1.48), although both sequential (HR 2.90; 90% CI 2.23-3.76) and concurrent (RR 1.48; 90% CI 1.11-1.97) therapies showed significant risk of LVEF decline in the trastuzumab groups.

The recent meta-analysis comparing adjuvant trastuzumab *versus* no trastuzumab in a sub-set of HER2 positive patients with either hormone receptor (HR) -positive or HR-negative disease, together with tumours $\leq$ 2 cm did not report on adverse effects.[25]

Comment:
Trastuzumab use is associated with an increased risk of cardiac toxicity (increased risk of CHF, LVEF decline); this risk increases with longer-duration therapies (i.e. over 6 months)[6,8.17.18.19]. There did not appear to be an increased risk of cardiac death with trastuzumab[6,21]. There was no difference in cardiac toxicity when trastuzumab was given concurrently or sequentially[11,24]. An increase in incidence of CNS recurrence was found with trastuzumab, however this was assumed to be due to increased survival in this group.[24]

Quality assessment

The assessment of methodological quality was difficult, as the details of methods used were not always provided. The trials included in the evaluation were randomised, open-label, phase 3 trials. A summary of the assessment of the quality of the trials evaluating the efficacy and safety of adjuvant trastuzumab for the treatment of breast cancer is provided in Annexure D.

Some key limitations and possible sources for bias were identified as follows:

- For the HERA follow-up trials (major study in this review) there was a protocol amendment from the original trial: Patients in the observation group with LVEF ≥55% who had not relapsed were crossed over to trastuzumab treatment (following results from original trial).[7, 10,16]

- The chemotherapy protocols in the HERA trials may have been suboptimal, as less than a third of the study population had received prior anthracycline and taxane therapy.[7, 10, 16]
- In the FinHER study distant DFS became the primary endpoint in the final analysis instead of recurrence-free survival, which was considered the primary endpoint in the first interim analysis.[11]
- There appeared to be a discrepancy in one series of trials, with an additional 5 patients in the 4-year and 8-year follow up compared to the initial trial.[7, 10, 16]
- The trials recruited women of varying risk profiles for cardiovascular disease. Trials included women with no cardiac risk factors or LVEF $\leq$ 50% to $\leq$ 55%, after completion of chemotherapy (with or without radiotherapy), prior to randomisation to trastuzumab or control.[7, 9, 10, 16] The data is thus not applicable to women with cardiac risk factors and an LVEF <50% after completion of chemotherapy with or without radiotherapy.
- The intervention group, trastuzumab plus standard treatment as adjuvant therapy was compared against the control group of standard treatment alone. Studies varied in terms of the co-administered regimens and standard treatments[11]. In two cases, the trials compared different trastuzumab-containing regimens: a comparison of concurrent *versus* sequential trastuzumab[9], and 1 year *versus* 2 years trastuzumab treatment.[8]
- Publication bias must be considered in two studies (HERA, N9831), where certain results for patient groups was not reported.[11]
- For the joint analysis of trials N9831 plus B-31, there were differences in patient eligibility (in N9831, women with high-risk, node negative disease were eligible, however, this was not so for B-31).[19-21]

Cost

A preliminary report of the cost-effectiveness of trastuzumab in the adjuvant setting was conducted, and three pricing options were investigated (refer to Annexure E for the detaiked costing report).

The price options were:

- R10 596,41/vial (Current Price)
- R6887,67 /vial (Previously Offered Price)
- R2000, 00/vial (Desirable Price)

The threshold for affordability is often quoted as 1 - 3 times Growth Domestic Product (GDP), with developing countries usually using not more than 1 times GDP. The South African GDP is approximately R100 000, and thus at the current offered price of R10

596.41 the analysis indicates that trastuzumab has an incremental cost-effectiveness ratio (ICER) of more than R100 000/QALY which may well be deemed not cost-effective.

Furthermore, the budget impact for treating less than 500 patients per annum is considerable. Even if the vial price is reduced to the previously offered price of R6 887.67, the budget impact is still in the region of R40 million in the first year.

At the desired price of R2 000 per vial, the budget impact will be in the region of R10 million in the first year, with a cost/QALYd of approximately R18 000, which could be considered more desirable.

Alternative adjuvant agents on the EML for HER2-positive breast cancer:
There are no similar agents on the EML for the indication of HER2 breast cancer.

Dosing of trastuzumab for HER2-positive using the 3-weekly schedule:
The initial loading dose of trastuzumab for the treatment of early and metastatic breast cancer in HER2-positive women is 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later, and then 6 mg/kg repeated at 3 weekly intervals.[23] Trastuzumab is administered as an infusion over approximately 90 minutes.[23] Thus, if treatment were administered for 1 year, this would result in a total of 18 doses of trastuzumab (1 loading dose and 17 follow-up maintenance doses).

Summary:
The evidence presented suggests that trastuzumab-containing regimens improves disease-free survival and overall survival in women with HER2-positive breast cancer, but increases risk of cardiac toxicities, such as LVEF decline and congestive cardiac failure.
Although a treatment course over 6 months was shown to have less cardiac toxicity than a 12-month course, it is non-inferior with regards to efficacy[8]. Concurrent (rather than sequential) adjunctive therapy with trastuzumab also appears to be more efficacious[9]. The results confirm that 1 year of adjuvant trastuzumab remains the standard of care for HER2-positive early breast cancer patients. The significant improvement in disease free survival and overall survival persists over time and the incidence of cardiac endpoints remains low at a median follow-up of 8 years.[7, 10, 16] This conclusion however must be carefully viewed against the limitations of the evidence identified and cost considerations presented in this review.

Suggested review indicators for consideration:

- Randomised controlled trials (RCTs) investigating the impact of shorter trastuzumab treatment periods on clinical effectiveness and safety.

- Randomised controlled trials investigating the optimal dosing schedule of trastuzumab treatment with different chemotherapy regimens.
- Long-term follow-up data of women who have been treated with trastuzumab.
- Studies that examine the risk of disease recurrence in specific subgroups (for example, those with nodal involvement, those with tumours with and without hormone receptors).
- Pricing changes, including introduction of generic products and biosimilars.
- Randomised controlled trials investigating the impact of trastuzumab *versus* novel agents on clinical effectiveness and safety.

Recommendation

Using the information from the National Essential Medicines List Committee (NEMLC) and the Pharmacoeconomic Evaluation Unit, the National Health Council (April 2017) recommended that Trastuzumab be made available for the adjuvant management of early stage breast cancer administered 3-weekly for a period of 12 months.

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Annexure A:
Summary of the current Package of Care for Breast Cancer on the National Essential Medicines List

Treatment	Drugs	Recommendations
Adjuvant chemotherapy	Standard of care: Cyclophosphamide, methotrexate, 5-fluorouracil for 6 months or doxorubicin, cyclophosphamide for 4 cycles	Cyclophosphamide Methotrexate 5-fluorouracil Doxorubicin
	Taxanes: docetaxel, paclitaxel	Under review: A decision on the use of taxanes for adjuvant therapy will be made after a cost benefit analysis is performed.
Metastatic/Advanced: first-line chemotherapy	Standard of care: Doxorubicin containing regimens: - 5-fluorouracil, doxorubicin, cyclophosphamide - doxorubicin, cyclophosphamide	Cyclophosphamide 5-fluoro-uracil Doxorubicin
	Taxanes	Not recommended.
Second-line Metastatic	Taxanes	Efficacy is acknowledged.
Hormonal therapy	Standard of care in ER positive breast cancer: tamoxifen	Tamoxifen Recommended for use as the first line agent in adjuvant and metastatic settings
	Aromatase inhibitors (AI): Anastrozole Letrozole Exemestane	Recommended for use in patients who failed tamoxifen therapy or who are intolerant to tamoxifen
	Medroxyprogesterone acetate	Replaced by AI in tamoxifen failure
	Long acting LHRH agonists Goserelin Buserelin Leuprolide	Recommended to achieve medical ovarian ablation in premenopauasal women in which an AI is required
Ancillary drugs	Bisphosphonates: Zoledronate Ibandronate Pamidronate	Recommended

LHRH - luteinizing hormone-releasing hormone