Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

30 April 2019

DEPARTMENT MEMORANDUM
No. 2019 - 0205

TO : **DIRECTORS OF CENTERS FOR HEALTH DEVELOPMENT, CHIEFS OF MEDICAL CENTERS, HOSPITALS, SANITARIA, EXECUTIVE DIRECTORS OF SPECIALTY HOSPITALS, MINISTRY OF HEALTH – BANGSAMORO AUTONOMOUS REGION IN MUSLIM MINDANAO (MOH-BARMM) AND OTHER CONCERNED**

SUBJECT : **Price Adjustment of the 2018 Edition of the Drug Price Reference Index (DPRI)**

In relation to the Drug Price Reference Index (DPRI) which aims to maximize government funds in the expenditure for essential medicines, the prices of following patented medicines are hereby corrected based on the most efficient procurement price of the government for 2018:

Drug name	2018 DPRI	Adjusted Price	Remarks
Rituximab 10 mg/mL, 10 mL vial	₱15,231.02	**₱16,754.12**	Lowest price (excluded from the 10% price variation)
Rituximab 10 mg/mL, 50 mL vial	₱74,661.35	**₱82,127.48**	Lowest price (excluded from the 10% price variation)
Trastuzumab 120 mg/mL, 5 mL	₱17,305.20	**₱26,000.00**	The Price is based on the negotiated price of the company with Disease Prevention and Controlled Bureau (DPCB) upon inclusion in the BCMAP

Accordingly, the list was updated and is now available online at www.dpri.doh.gov.ph. Attached herewith is the latest copy which your institution can use in your future procurement. However, for all the ongoing procurement, they may proceed using the DPRI edition stated in Department Memorandum No. 2018-0379 and Department Memorandum No. 2019-0055.

In light of the above, all DOH Centers for Health Development and the MOH-Bangsamoro Autonomous Region in Muslim Mindanao are hereby directed to disseminate this information to all DOH Retained and Specialty Hospitals and Local Government Units, and extend necessary assistance thereof. Distribution of hard copies will follow once printed.

For any concerns or inquiries, you may contact Mr. Achilles V. Aragona or Mr. John Lester Custodio at (02) 875-7734 or 875-7264 local 253.

For strict and prompt compliance.

By the Authority of the Secretary of Health:

ROLANDO ENRIQUE D. DOMINGO, MD, DPBO
Undersecretary of Health
Health Regulation Team

5/30/19

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PROPOSAL FORM FOR INCLUSION OF TRASTUZUMAB SC IN BCMAP

A. GENERAL INFORMATION ON TRASTUZUMAB SC:

GENERIC NAME	**Trastuzumab**
BRAND NAME (if any)	**Herceptin®**
THERAPEUTIC CLASSIFICATION	**Antineoplastic agent (Monoclonal Antibody)**
INDICATION	• **HER2-positive Early Breast Cancer (eBC)** • **HER2-positive Metastatic Breast Cancer (mBC)**
DOSAGE FORM/ STRENGTH	• **Fixed dose 600 mg/5ml fixed dose vial containing solution for injection (Subcutaneous (SC) formulation)**
ROUTE OF ADMINISTRATION	• **Subcutaneous (SC) Injection**

DOSE, FREQUENCY AND DURATION OF ADMINISTRATION	• **The recommended fixed dose of Herceptin SC is 600 mg every three weeks irrespective of the patient's body weight.**
	• **This dose should be administered in 2-5 minutes every three weeks**
	• **Duration of therapy**
	  ○ **eBC: 18 cycles every 3 weeks or 1 year**
	  ○ **mBC: until disease progression**

MANUFACTURER	**F. Hoffman-La Roche, Ltd.** **Wurmisweg, 4303 Kaiseraugst, Switzerland**
IMPORTER/ TRADER	**Roche (Philippines), Inc.** **One Global Place 5th Ave corner 25th St. BGC, Taguig City**
DISTRIBUTOR	**Zuellig Pharma Philippines, Inc.**

B. SUMMARY OF JUSTIFICATION FOR INCLUSION:

The proposed medicine should fulfill ALL of the following criteria:	**JUSTIFICATION AND REFERENCES**
☑ **It has proven safety**	**Results from the following clinical trials demonstrate comparable safety profile between Trastuzumab IV and Trastuzumab SC:** **Reference 1:** ***Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a Phase III, open-label, multicenter, randomized trial. Lancet Oncol 2012; 13: 869–78.*** • A head to head phase III trial was conducted to compare the safety of Trastuzumab IV, the currently listed medicine in PNF with Tratuzumab SC, a new formulation with a different route of administration in the same indication (early BC).

	• The number of patients experiencing an adverse event of any grade was comparable between the intravenous trastuzumab and subcutaneous trastuzumab groups. The most common adverse events of any grade (>25% in either group) were alopecia (62·8% [187 of 298] in the intravenous group vs 62·6% [186 of 297] in the subcutaneous group), nausea (48·7% [145 of 298] vs 48·5% [144 of 297]), neutropenia (46·3% [138 of 298] vs 44·1% [131 of 297]), diarrhoea (36·6% [109 of 298] vs 33·7% [100 of 297]), asthenia (25·2% [75 of 298] vs 24·6% [73 of 297]), and fatigue (26·5% [79 of 298] vs 22·6% [67 of 297]). The same proportion of patients (52%) in each group had a severe adverse event. The pattern of severe adverse events was comparable between study groups. Most grade 3 or worse adverse events were hematological toxic effects, followed by gastrointestinal disorders. The most common severe adverse events were neutropenia, leucopenia, and febrile neutropenia. **Reference 2:** ***Pivot X, Gligarov J, Muller V, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol 2013; 14: 962–70.*** • During the pooled subcutaneous and intravenous periods, 164 of 244 (67·2%) patients experienced at least one adverse event, and most were grade 1 (148 [60.7%]) or grade 2 (78 [32.0%]). Grade 3 events were reported in 11 (4·5%) patients, and no patient had a grade 4 or 5 adverse event. Arthralgia (21 [8·6%] patients), and localised injection site reactions (19 [7·8%] patients) were the most common events overall, with influenza being the most common grade 3 adverse event (two [0·8%] patients). Differences between rates in the pooled subcutaneous and intravenous periods were driven by grade 1 events occurring more frequently during the subcutaneous period. The main driver of differences in grade 1 events was localised reactions in the injection site. All injection site reactions and systemic administration-related reactions were grade 1 or 2. Serious adverse events were reported in six of 244 patients (2·5%, events reported: mental crisis, axilla abscess, expander infection, and haematoma during the subcutaneous period, and influenza and fibroadenoma during the intravenous period), none of which were considered to be related to trastuzumab and each was resolved completely. Study drug discontinuations due to adverse events occurred in two (0·8%) patients during the subcutaneous period and one (0·4%) patient during the intravenous period. All reported cardiac events were grade 1 or 2 and none were serious. Ejection fraction decreases or left-ventricular dysfunctions were reported in five (2·1%) of 236 patients during the subcutaneous period and one (0·4%) during the intravenous period. All were considered to be related to the study drug and all were fully resolved except one of case grade2 left-ventricular dysfunction, which was ongoing at the time of analysis. **Reference 3:** ***Gligorov J, Beyhan A, Verrill M, et al.***

	SafeHer Phase III study primary analysis: Safety of subcutaneous trastuzumab plus chemotherapy for early breast cancer. Abtract 326. Eur Br Can Congress, 10 Mar 2016. • AE rates varied according to the timing of chemotherapy, with higher AE rates in the concurrent chemotherapy subgroups. • Blood and lymphatic system disorders were the most common types of ≥grade 3 AEs reported. • Grade ≥3 cardiac disorders were reported in 21 (1.1%) and three (0.4%) patients in Cohorts A [Herceptin SC vial) and B [Herceptin single-use injection device], respectively. • The most common cardiac disorders of any grade were palpitations (40 patients in Cohort A [2.1%] and 15 [2.1%] in Cohort B) and mitral valve incompetence (37 [2.0%] and 15 [2.1%] patients, respectively). • Injection site reactions were reported in 378 patients (20.3%) in Cohort A and 138 (19.5%) in Cohort B, at any grade. • In the subgroup of patients who received concurrent chemotherapy, AEs were more common during the actual period of concurrent chemotherapy compared with the period when patients did not receive concurrent chemotherapy in both cohorts.
☑ **It has proven efficacy**	***Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a Phase III, open-label, multicenter, randomized trial. Lancet Oncol 2012; 13: 869–78.*** • A head to head phase III trial was conducted to compare the efficacy of Trastuzumab IV, the currently listed medicine in PNF with Tratuzumab SC, a new formulation with a different route of administration in the same indication (early BC). • Results show that Herceptin® SC provides comparable pharmacokinetics and efficacy to Herceptin® IV with non-inferiority demonstrated for both co-primary endpoints. • Subcutaneous trastuzumab was non-inferior to intravenous trastuzumab in terms of the proportion of patients who achieved pCR: 118 (45·4%) of 260 patients in the subcutaneous group and 107 (40·7%) of 263 in the intravenous group. The difference between groups (subcutaneous minus intravenous) was 4·7% (95% CI –4·0 to 13·4); the lower limit of the two-sided 95% CI for the difference was greater than the pre-specified non-inferiority margin (–12·5%). • The proportion of patients who achieved pCR in the intention-to-treat population was consistent with that obtained in the per-protocol population: pCR was achieved by 124 (42·2%, 95% CI 36·5–48·0) of 294 patients in the subcutaneous group and 111 (37·4%, 31·9–43·1) of 297 in the intravenous group. • Similar results were seen for tpCR (including response in the axilla; difference between groups 5·0%, 95% CI –3·5 to 13·5). Multiple logistic regression analysis of pCR, adjusting for stratification

	factors and selected baseline characteristics, was in line with the corresponding unadjusted results, and no interaction between bodyweight and pCR was detected. • The proportion of patients who achieved an overall response was much the same in the intravenous and subcutaneous groups and the median time to response was much the same in both treatment groups. Efficacy results in the intention-to-treat population were consistent with those obtained in the per-protocol population.
☑ **There is no other medicine listed in the formulary which is indicated for the same condition.**	Trastuzumab 150 mg intravenous (IV) formulation is listed in the Philippine National Formulary. The availability of Trastuzumab Subcutaneous (SC) Formulation offers the full benefit of Trastuzumab IV with the added advantage of improved compliance, convenience and cost advantage versus IV formulation: • Trastuzumab SC: Ready to use, liquid formulation. o Trastuzumab SC is administered as a 600 mg fixed dose, regardless of body weight and without loading doses delivered in 2-5 minutes subcutaneously. o More time for HCPs to attend to other patients • Trastuzumab 150 mg lyophilized powder for concentrate for solution for intravenous infusion. Reconstitution and dilution is required in preparing the solution for infusion. o Trastuzumab IV is weight-based requiring dose computations according to individual patient body weight. Such dose adjustment may be associated with potential vial wastage, increased resource time utilization and potential errors. o Administration time is 30- 90 minutes, meaning that a considerable amount of time is spent in infusion chairs by the patient over the full treatment course of 1 year for patients receiving treatment in eBC.
☑ **It will be used for an urgent health situation defined as immediately requiring treatment to prevent death, permanent disability or major or permanent organ dysfunction (specify situation);**	**1. Why is the situation urgent?** • HER2-positive breast cancer is an aggressive form of breast cancer and if left untreated, it is linked to poor chance of survival. • The availability of Trastuzumab SC offers the full efficacy and safety benefits of Trastuzumab IV and will also mean potential cost savings for patients and the institution: o Potential Cost Savings: Trastuzumab SC administration of Trastuzumab may lead to a substantial reduction in active HCP time, patient chair and unit time, consumable use and overall costs. o Practical advantages in terms of patient compliance since no IV access device needed to receive Trastuzumab SC as well as medical resource utilization (MRU) (including equipment, resources (eg. infusion capacity may be released) and time required, for both HCPs and patients). o Since this is given subcutaneously, there is no need to establish IV access, an important consideration for patients who have already received multiple doses of chemotherapy.

	(References: 1. Wolff A, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31(31):3997-4013. 2. Slamon D, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365(14):1273-83) **2. What is the ranking of the disease relative to other disease conditions in the health facility?** • Average breast cancer incidence at EAMC is 178 per month or 2,136 cases a year. Approximately 20% will turn out to be HER2-positive. • Breast cancer is the ranked #1 as most common cancer for both sexes in the Philippines. *(Reference: Globocan 2012 http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed 24 July 2017)* **3. What is the potential for spread of the disease?** • Breast cancer is not contagious but there risk factors in the development of breast cancer.

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

Instruction: Please gather data on the price of the proposed medicine from the pharmaceutical company. For the comparator drug, please refer to the Drug Price Reference Index (DPRI).

PARAMETER (Indicate information for intended recipient)* *INTENDED RECIPIENT:* HER2-POSITIVE BREAST CANCER	NEW FORMULATION AND ROUTE OF ADMINISTRATION HERCEPTIN SC (Fixed Dose)	CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF OR STANDARD OF CARE HERCEPTIN IV (Weight-Based)	REFERENCES
UNIT COST OF MEDICINE[A]	1 vial fixed dose **PHP26,000/cycle**	Cycle 1 (Loading dose of 3 vials): PHP 39,000/cycle1 Cycle 2-18 (subsequent 2 vials): PHP26,000/cycle (2 vials)	Herceptin IV and Herceptin SC based on list price
NUMBER OF DOSAGE UNITS PER UNIT COURSE[B]	600 mg/cycle	400 mg/cycle 1 300 mg for cycle 2-18	Based on average 50 kg body weight
DURATION OF TREATMENT[C]	18 Cycles every 3 weeks (adjuvant setting)	18 Cycles every 3 weeks (adjuvant setting)	Trastuzumab Prescribing Information, Roche (Philippines) Inc. Current at February 2015
TOTAL COST PER PATIENT[D] **Formula: A x B x C**	**PHP 468,000**	**PHP 481,000**	
OTHER MEDICAL COSTS ASSOCIATED WITH THE USE OF THE DRUG[E] **a. Implementation costs: - cost of drug administration (e.g., syringe, diluent) monitoring (.e.g, PT, PTT), additional diagnostic services (e.g., Xray, CT scan), additional equipment** **b. Intervention costs: (management of adverse drug reaction treatment)**	**Implementation cost Drug administration (per cycle)** 1. Transfer needle 21 G – 1 x 5 = PHP 5 2. Injection needle 25 or 27 G – 1 x 5 = PHP 5 3. Syringe (5 ml) – 1 x 10 = PHP 10 4. Pair of sterile gloves – 70 x 1 = PHP 70 5. Paracetamol 500 mg/tab – 0.23 x 3 = PHP 0.69 6. Diphenhydramine 50 mg/tab – 1 x PHP0.90 = PHP 0.90 7. alcohol swab – 15 x 1 = PHP 15	**Implementation costs Drug administration (per cycle)** 1. pNSS 500 cc glass bottle – 45 x 1 = PHP 45 2. pNSS 500 cc plastic bottle – 45 x 1 = PHP 45 3. Macroset – 400 x 1 = PHP 400 4. Needle G18 – 5 x 1 = PHP 5 5. 10-cc syringe – 10 x 1 = PHP 10 6. IV cannula G22/G24 – 200 x 1 = PHP 200 7. Diphenhydramine 50 mg/vial – 1xPHP 0.90 = PHP .90 8. Paracetamol 500 mg/tab – 0.23 x 3 = PHP	**DPRI** Paracetamol 500 – PHP 0.23 Diphenhydramine – PHP 0.90 9% Sodium Chloride – PHP 45.00 SterileWater for Injection – PHP 22

	Subtotal: PHP 106.59 x 18 = PHP 1,918.62 8. Infusion room fee: 1st to 18th cycle - 400/hr X 1 hr = PHP 400 x 18 Subtotal: PHP 7,200 9. Professional fee: 5,000 x 18 = PHP 90,000 **Monitoring/diagnostics** Two-dimensional echocardiography at baseline and every 3 months during treatment – 2,000 x 7 = PHP 14,000 **Implementation cost (a) =PHP 113,118.62** **Intervention Costs (b) Usually none** **TOTAL: PHP 113,118.62**	0.69 9. Pair of sterile gloves – 70 x 1 = PHP 70 10. Sterile water for injection 50 mL – 22 x 1 = PHP 22 11. Alcohol swab – 15 x 1 = PHP 15 **Subtotal: PHP 813.59 x 18 = PHP 14,644.62** 12. Infusion room fee: 1st cycle - 400/hr X 3 hrs = 1,200 2nd to 18th cycle – 400/hr x 2 hrs = 800 Subtotal: PHP 14,800 13. Professional fee: 5,000 x 18 = PHP 90,000 **Monitoring/diagnostics** Two-dimensional echocardiography at baseline and every 3 months during treatment – 2,000 x 7 = PHP 14,000 **Implementation Cost (a) =PHP 120,644.62** **Intervention Costs (b) Usually none** **TOTAL: PHP 120,644.62**	
TOTAL TREATMENT COST PER PATIENT[F] Formula: D + E	**PHP 581,118.62**	**PHP 601,644.62**	
EXPECTED NUMBER OF PATIENTS WHO WILL USE THE DRUG [G] **Possible references:** • **Burden of Disease** • **If no local epidemiological study, current volume of use in the Philippines based on market data**			**Phiippine Cancer Society Data**
ESTIMATED BUDGET IMPACT Formula: F x G			