Herceptin Dosing and Administration Recommendations

This article responds to your request for information on Herceptin® (trastuzumab) and dosing and administration recommendations.

Please refer to the locally approved dosing information provided in the Herceptin prescribing information. Any deviation from this information is considered off-label and any treatment decisions based on such deviations are the full responsibility of the prescribing physician.

In brief

- Recommended Herceptin IV doses are based on bodyweight, schedule, and whether the patient requires a loading or maintenance dose.
    - A patient may require to be readministered a loading dose following a delayed or missed dose.
    - Roche/Genentech does not have recommendations on initial Herceptin IV doses when switching from other therapies, including Herceptin Hylecta ™ (trastuzumab and hyaluronidase), Phesgo® (trastuzumab, pertuzumab, and hyaluronidase) and Kadcyla® (trastuzumab emtansines), however experience from clinical trials is available.
- No dose adjustments were required for Herceptin IV for obese or underweight patients in clinical trials. Patients were dosed on actual body weight, with no upper or lower limit.
    - In clinical trials a 10% change in weight would require a patient's dose to be recalculated.
- There is currently no global consensus regarding the length of time to observe patients following administration of Herceptin.
    - Where included, observation times should be according to the local Herceptin prescribing information or package insert.
    - If local prescribing information does not stipulate an observation time, this should be in line with local guidelines or best practice.

Administering premedications

Premedications are not required prior to administration of Herceptin, however they may be used to reduce the risk of the occurrence of infusion related reactions, in line with local clinical practice.[1]

Recommended Herceptin loading and maintenance doses

The recommended loading and maintenance doses of Herceptin IV are outlined in Table 1.[1]

Table 1. Loading and maintenance doses by schedule

If the dosing schedule is...	then the loading dose is...	and the maintenance dose is...
weekly	4 mg/kg over 90-minutes	2 mg/kg over 30-minutes if prior dose was well tolerated

every 3 weeks	8 mg/kg over 90 minutes	6 mg/kg over 30-minutes if prior dose was well tolerated

Reloading following delayed or missed doses

If a patient experiences a missed dose or dose delay, the next dose should be administered as soon as possible.[1] Do not wait until the next planned dose.

Depending on the time between the two sequential doses, the patient may require a loading dose before returning to the maintenance dose schedule.[1] Refer to Table 2 for recommendations on re-loading Herceptin IV.

Table 2. Recommendations regarding delayed or missed doses

If the dosing schedule is...	and the time between the two sequential doses is...	then administer a...
weekly	two weeks or less	maintenance dose — Herceptin IV 2 mg/kg over 30-minutes, if the prior dose was well tolerated
	more than 2 weeks	loading dose — Herceptin IV 4 mg/kg over 90-minutes
every 3 weeks	four weeks or less	maintenance dose — Herceptin IV 6 mg/kg over 30-minutes if prior dose was well tolerated
	more than 4 weeks	loading dose — Herceptin IV 8 mg/kg over 90 minutes

In patients also being treated with Perjeta

The Perjeta® (pertuzumab) prescribing information advises that a re-loading dose of Herceptin IV is only required if the time between sequential Herceptin and Perjeta doses is greater or equal to 6 weeks, or a dose is missed by 3 or more weeks.[2]

The re-loading doses and intervals recommendations are based on the pivotal clinical trials for Herceptin or Perjeta and Herceptin, respectively.[1,2]

In the Perjeta clinical trials, a longer duration between doses of Herceptin IV was permitted when it was given in combination with Perjeta.[3] This allowed for more convenience of the scheduling of dosing for physicians and patients.

Switching from other therapies to Herceptin IV

Switching from Herceptin Hylecta

Roche/Genentech has no recommendation for how to dose Herceptin IV in patients who are switched from Herceptin Hylecta, beyond the approved dosing regimen.[1]

Treatment protocol in the PrefHER study

Switching treatment from Herceptin IV to Herceptin Hylecta and vice versa, using the every 3 week dosing regimen, was investigated in the PrefHER study.[4] In this trial, when patients were switched from the subcutaneous formulation to the intravenous formulation, they were given the maintenance dose of 6

mg/kg for their initial IV dose, provided that not more than one week had passed from the expected dosing date.

Switching from Phesgo

Roche/Genentech has no recommendation for how to dose Herceptin IV in patients who are switching from Phesgo, beyond the approved dosing regimen.

Treatment protocol in the PHranceSCa study

The Phase 2 PHranceSCa study evaluated patient preference of Phesgo, a fixed-dose subcutaneous injection combination of pertuzumab, trastuzumab and hyaluronidase, compared with IV Herceptin and IV Perjeta in the treatment of early HER2 positive breast cancer in the adjuvant setting.[5] In one arm of the study, patients were administered 3 cycles of Phesgo every 3 weeks and then switched to receive 3 cycles of IV Perjeta and IV Herceptin every 3 weeks.

The initial dose of Herceptin IV after the switch from Phesgo was given at the maintenance dose of 6 mg/kg, unless it had been more than 6 weeks since their last treatment, in which case the loading dose of 8 mg/kg was administered.[5]

Switching from Kadcyla

Roche/Genentech has no recommendation for how to dose Herceptin IV in patients who are switching from Kadcyla, beyond the approved dosing regimen.

Treatment protocol in the KATHERINE study

The Phase 3 KATHERINE study evaluated the efficacy and safety of adjuvant Kadcyla compared to Herceptin in early HER2 positive breast cancer.[6] Both Kadcyla and Herceptin were dosed for 14 cycles, with a three-weekly dosing interval.

In the study, patients who discontinued Kadcyla due to adverse events were allowed to switch to treatment with Herceptin IV in order to complete 14 cycles of anti-HER2 therapy.[6] Those patients received their first dose of Herceptin at the start of the next treatment cycle or after the adverse event had resolved, in each case with the initial loading dose of 8mg/kg of Herceptin, followed by 6mg/kg every 3 weeks.[7]

Table 3. Initial dose of Herceptin IV after switching from other treatment in clinical trials

Switching from	Initial dose of Herceptin IV in clinical trials
Herceptin Hylecta	6 mg/kg, unless it had been more than 4 weeks since the last dose of Herceptin SC[4]
Phesgo	6 mg/kg, unless it had been more than 4 weeks since the last dose of Phesgo[5]
Kadcyla	8 mg/kg of Herceptin, followed by 6 mg/kg every 3 weeks[7]

Switching from trastuzumab biosimilars

Alternating or switching between Herceptin and products that are biosimilar but not deemed interchangeable requires the consent of the prescribing physician.[1] The benefits and risks needs to be carefully considered when the safety and efficacy of alternating or switching has not been established.

Roche/Genentech has no recommendations for how to dose Herceptin IV when switching from trastuzumab biosimilars, therefore the decision on dosing would be the responsibility of the prescribing

physician. Roche/Genentech recommends contacting the manufacturer of the trastuzumab biosimilar for any pharmacokinetic or safety information they have regarding switching between their product and Herceptin.

Sequence of Herceptin administration with chemotherapy

In 2 pivotal adjuvant breast cancer trials where Herceptin was administered concurrently with paclitaxel (N9831 and B-31 trials), Herceptin was given after paclitaxel.[8]

In the BCIRG 006 study, adjuvant docetaxel was administered prior to Herceptin for days on which both agents were administered.[9] For the other Herceptin-containing arm, docetaxel was administered first, followed by carboplatin, and then Herceptin for days on which the three agents were scheduled to be given.

In the pivotal, Phase 3 study in metastatic breast cancer patients, the initial dose of Herceptin preceded the first dose of chemotherapy by 24 hours; however, subsequent doses of Herceptin were administered immediately prior to chemotherapy (i.e., on the same day), provided the initial dose of Herceptin was well tolerated.[10]

In the pivotal, Phase 3 study (ToGA) in metastatic gastric cancer patients, cisplatin could be administered 30 minutes after the end of Herceptin infusion on Day 1 of each treatment cycle.[11]

Weight-based dosing considerations from clinical trial experience

In over- or underweight patients

No Herceptin dosage adjustments were required for Herceptin IV for obese or underweight patients in clinical trials. Patients were dosed on actual body weight, with no upper or lower limit.[9,11-13]

In patients experiencing weight change

The frequency at which patients were weighed varied between Herceptin IV trials, and included one, two and three week intervals.[9,11,12] Typically, a 10% change in body weight from baseline would require a patient's dose to be recalculated.[9,11,13]

Recommended observation times

There is currently no global consensus regarding the length of time to observe patients following administration of Herceptin. Where included, observation times should be according to the local Herceptin prescribing information. If local prescribing information does not stipulate an observation time, this should be in line with local guidelines or best practice.

Recommended observation times for Herceptin IV

A post-infusion-initiation observation period for Herceptin IV is recommended in the United Kingdom and all European Union (EU) approved labels for Herceptin IV.[14,15]

- First infusion — 6 hours
- Subsequent infusions — 2 hours

Rationale for observation times

The recommended observation period was made by the EU following a review of updated safety information submitted to the European Medicine Agency (EMA), as part of a license renewal for Herceptin

in 2005.[16,17] The EMA requested a quantifiable observation time to be included in the European SmPC, which resulted in the inclusion of the 6 hour and 2 hour recommendations.[17,18]

Difference in recommended observation times between Herceptin Hylecta and IV

A post-administration-initiation observation period for Herceptin Hylecta is recommended in the EU label:[14]

- First injection — 30 minutes
- Subsequent injections — 15 minutes

The recommended observation period for Herceptin Hylecta was shortened from the previous recommendation of 6 and 2 hours, respectively, in the June 2021 update of the EU SmPC.[19] The reduction was made based on data from the Phase 3 SafeHER study which assessed the safety of assisted and self-administered Herceptin Hylecta for adjuvant treatment of early HER2 positive breast cancer.

It was determined from the study that overall adverse events, including administration-related reactions and injection site reactions, that occurred during the previous observation time were at a low rate and low grade, with the majority of the events reported as mild to moderate in intensity.[20]

The new observation time of 30 minutes for the first injection and 15 minutes for subsequent injections covers the majority of adverse events, including administration-related reactions and injection site reactions, reported during the previous observation time the study.[20] Patient safety is maintained with the reduced observation time.[20]

Herceptin dosing and administration recommendations references

1. Roche Internal Regulatory Report. Accessed 14 June 2023.

2. Roche Internal Regulatory Report. Accessed 14 June 2023 .

3. Roche Internal Communication. Accessed on 11 July 2023.

4. Roche Internal Clinical Report (PrefHER). Accessed 05 July 2023.

5. O'Shaughnessy J, Sousa S, Cruz J, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): A randomised, open-label phase II study. Eur J Cancer 2021;152:223-232. https://www.ncbi.nlm.nih.gov/pubmed/34147014

6. von MG, Huang C, Mano M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617-628. https://www.ncbi.nlm.nih.gov/pubmed/30516102

7. Roche Internal Clinical Report (KATHERINE). Accessed 05 July 2023.

8. Roche Internal Clinical Report (Joint analysis). Accessed 9 Oct 2023.

9. Protocol for Adjuvant trastuzumab in HER2-positive breast cancer. October 6, 2011. Available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa0910383/suppl_file/nejmoa0910383_protocol.pdf. Accessed on November 30, 2023.

10. FDA clinical review of BLA 98-0369 - Herceptin - trastuzumab:35. Food and Drug Administration 2011;http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

11. Roche Internal Clinical Report (ToGA). Accessed 2 August 2023.

12. Roche Internal Clinical Report (H0649g). Accessed 2 August 2023.

13. Roche Internal Clinical Report (HERA). Accessed 2 August 2023.

14. Herceptin Summary of Product Characteristics. March 17, 2023. Available at https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf. Accessed on June 20, 2023.

15. Herceptin 150mg Powder for concentrate for solution for infusion SmPC. September 28, 2021. Available at https://www.medicines.org.uk/emc/product/3856. Accessed on June 20, 2023.

16. Herceptin: EPAR - Scientific Discussion. October 21, 2005. Available at https://www.ema.europa.eu/en/documents/scientific-discussion/herceptin-epar-scientific-discussion_en.pdf. Accessed on June 20, 2023.

17. Roche Internal Correspondence. Accessed 25 July 2023.

18. Roche Internal Regulatory Report. Accessed 25 July 2023.

19. Herceptin: EPAR - Procedural steps taken and scientific information after authorisation. April 18, 2023. Available at https://www.ema.europa.eu/en/documents/procedural-steps-after/herceptin-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed on June 21, 2023.

20. Roche Internal Clinical Report (SafeHER). Accessed 05 July 2023 .