

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219469Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA IQA Template Title Page- EXEC SUMMARY		
Document ID:	OPQ-ALL-TEM-0040		
Effective Date:	26 Sep 2023	Revision:	00
Total Pages:	5		



Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA) Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	219469
Applicant Name	Bayer Healthcare Pharmaceuticals Inc.
Drug Product Name	LYNKUET® (elinzanetant) Capsule, 60 mg
Dosage Form	Capsule
Proposed Strength(s)	60 mg
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	120 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of moderate to severe vasomotor symptoms associated with menopause
Drug Product Description	Bayer Healthcare Pharmaceuticals Inc. has submitted this 505(b)(1) new drug application for LYNKUET® (elinzanetant) Capsule, 60 mg indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause. The patients are to take two 60 mg capsules (total of 120 mg) prior to bedtime. The active ingredients, elinzanetant is a NK-1/NK-3 receptor antagonist. Elinzanetant has not been previously approved or marketed as a drug in the United States and therefore, it is classified as a New Molecular Entity (NME). LYNKUET capsules are oblong, opaque-red, soft-gel capsules printed with "EZN60" in white ink. Each capsule contains 60 mg of elinzanetant as the active ingredient and caprylocaproyl macrogolglycerides, glycerol monocaprylocaprate, glycerol mono-oleate, polysorbate 80 and all-rac-α-tocopherol as inactive ingredients. All excipients are within IID limits of

	previously approved drug products for oral use. An appropriate BSE/TSE free statement for the gelatin capsule has been submitted to the application. LYNKUET® (elinzanetant) capsule are packaged as two capsules in a blister, supplied in a blister cards with 6 blisters with a total 12 capsules per blister card. This drug product is also supplied as 5 blister card in a carton. LYNKUET® capsules should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Based on the stability data provided in this application an expiration dating period of 30 months is granted to this drug product.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C – 25°C (68°F -77°F); excursion permitted 15°C – 30°C (59°F -86°F) [see USP Controlled Room Temperature]		
Review Team	Discipline	Primary	Secondary
	Drug Substance	Friedrich Burnett, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Hitesh Shroff, PhD	Hamid Shafiei, PhD/Julia Pinto, PhD
	Manufacturing	Mesfin Abdi, PhD	Vaikunth Prabhu, PhD
	Biopharmaceutics	Kalpana Paudel, PhD	Tapash Ghosh, PhD
	Microbiology	N/A	N/A
	Environmental Assessment	Xiaoqin Wu, PhD	James Laurenson, PhD
	RBPM	Stephani Negan, MPH	
	ATL	Hamid Shafiei, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

This application has been recommended for approval from all OPQ disciplines. For this application, the environmental assessment and FONSI have been reviewed by the EA Team and are provided in Chapter III of this Integrated Quality Assessment (IQA). The OPQ's recommended CMC PI labeling as well as container and carton labels changes/revisions was communicated through the Clinical Team to the Applicant. The applicant has accepted all OPQ's recommended CMC changes/revisions to labeling/labels and has committed to submit the final agreed labeling/labels that reflects all OPQ's recommended changes/revisions prior to the PDUFA action date. Therefore, no labeling/labels review addendum will be included in this IQA, and the labeling/labels are now considered adequate.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, elinzanetant and the drug product, LYNKUET® (elinzanetant) Capsule, 60 mg.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC recommended changes/revisions to the PI labeling as well as container and carton labels have been communicated through the Clinical Review Team to the applicant and the recommended CMC changes/revisions have been accepted by the applicant.
- The applicant's environmental assessment and FONSI for this application have been reviewed by the OPQ Environmental Assessment Team and have been found adequate to support the approval of this application.

Therefore, this application is recommended for approval from the OPQ perspective with an expiration dating period of 30 months.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate

Biopharmaceutics - Adequate
Microbiology - N/A

Environmental Assessment: Review & FONSI - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ



Hamid
Shafiei

Digitally signed by Hamid Shafiei

Date: 3/26/2025 10:16:06AM

GUID: 507d824300005f344cf8b5e5989f0057

CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

1. Summary

Bayer Healthcare Pharmaceuticals Inc. initially proposed and discussed with FDA about a plan of submitting an environmental assessment (EA) for elinzanetant during the IND phase (IND 129492). Bayer then submitted an EA in the original NDA 219469 ORIG-1 for the drug product elinzanetant (60 mg soft capsule), which is for the treatment of moderate to severe vasomotor symptoms associated with menopause. The calculated screening-level expected introduction concentration (EIC) of the active pharmaceutical ingredient (API) elinzanetant in the aquatic environment was (b) (4) ppb and the refined EIC was (b) (4) ppb, both below the categorical exclusion level of 1 ppb; nevertheless, Bayer considered that the extraordinary circumstances could not be excluded due to the potential endocrine-related activity of elinzanetant. Therefore, Bayer decided to prepare an EA including a series of studies on environmental fate and effects of elinzanetant, per 21 CFR 25 and FDA 2016 guidance [1].

FDA reviewed and assessed the original EA, noting an incorrect calculation of the EIC of elinzanetant in the terrestrial (soil) environment. FDA also raised a concern over the aquatic predicted no effect concentration (PNEC) value of elinzanetant from the zebrafish extended one generation reproduction test (ZEOGRT), particularly an insufficient justification for excluding the fertilization rate as a population relevant toxicity endpoint for elinzanetant. To address FDA's concerns, Bayer submitted additional information in their subsequent responses to FDA's information requests (IRs), including the correction of the EIC (soil) and updated risk assessment of elinzanetant in the terrestrial environment, and a sufficient justification of the aquatic PNEC value of (b) (4) ppb.

After careful review and assessment, FDA concludes that the submitted information is sufficient to enable the Agency to determine whether approval of this drug product application may significantly affect the environment, and thus the EA is adequate for approval, per 21 CFR 25.15 (a). Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

2. Substance of Interest

Elinzanetant was identified as the only substance of interest in this EA. Elinzanetant is a non-hormonal, selective neurokinin 1 (NK-1) and 3 (NK-3) receptor antagonist that blocks NK-1 and NK-3 receptors signaling on kisspeptin/neurokinin B/dynorphin (KNDy) neurons to modulate neuronal activity involved in thermo- and sleep regulation. NK-1 and NK-3 receptors are also present in other species including fish, and their potential role in the reproductive axis in fish has been postulated.

Besides elinzanetant, the drug product also contains the following excipients:

- Capsule fill: all-rac- α -tocopherol, caprylocaproyl macroglycerides, glycerol, monocaprylocaprate, glycerol mono-oleate, and polysorbate 80.
- Capsule shell: ferric oxide red, ferric oxide yellow, gelatin, sorbitol special-glycerin blend, and titanium dioxide.
- Printing ink: ammonia solution, concentrated isopropyl alcohol, macrogol 400, polyvinyl acetate phthalate, propylene glycol, purified water, SDA 35A alcohol, and titanium dioxide.

Bayer stated that no novel excipients were used in the manufacture.

3. Expected Introduction Concentration (EIC)

Bayer estimated the highest amount of elinzanetant forecasted in 2029 to be (b) (4) kg/year and provided a justification to support this estimate. The EIC (water) and EIC (soil) were calculated based on this estimate.

3.1 EIC (water) and refined EIC (water) of elinzanetant

Bayer calculated the screening-level EIC (water) of elinzanetant to be (b) (4) ppb, following the FDA 1998 guidance [2]. To refine the EIC (water), Bayer considered potential reductions due to human metabolism and wastewater treatment plant (WWTP) removal. According to the submitted information, elinzanetant can be extensively metabolized in humans and the three major metabolites in human excreta have pharmacological activities comparable to that of the parent compound. The activity of other minor metabolites is unknown and considered similar to elinzanetant as a worst-case. Bayer concluded that the EIC (water) could not be further refined based on the human metabolism data, and the metabolism factor (MF) was set to (b) (4). To estimate WWTP removal, Bayer used the SimpleTreat software (v4.1.0) to predict the behavior of elinzanetant during the wastewater treatment process. Results showed that the emission of elinzanetant to WWTP effluent was (b) (4)%, and the remaining elinzanetant (i.e., (b) (4)%) was bound to sludge and retained in the WWTP. Loss to the atmosphere, i.e., mineralization to CO₂, was not expected. Bayer accordingly concluded that the EIC

(water) of elinzanetant could be refined by considering a depletion factor (DF) of (b) (4). Overall, based on the MF of (b) (4) and DF of (b) (4), Bayer calculated the refined EIC (water) of elinzanetant as (b) (4) ppb.

3.2 EIC (soil) of elinzanetant

Bayer calculated the EIC (biosolids) of elinzanetant based on the estimated production of (b) (4) kg/year and biosolids generation amount of (b) (4) kg/year in the U.S. The partition of elinzanetant to wastewater was not considered, i.e., assuming 100% of elinzanetant were distributed to sludge during the wastewater treatment process. Bayer then calculated the EIC (soil) of elinzanetant to be (b) (4) mg/kg dry weight (dw), following the EMA 2024 guidance [3] as recommended by FDA, and using a biosolids application rate of 20 tons/acre (i.e., 4.5 kg/m²) which is the upper end of typical biosolid application rates for agricultural land in the U.S. [4]. Bayer also calculated a high-end EIC (soil) using the highest biosolids application rate of 100 tons/acre (i.e., 22.4 kg/m²) [4] as recommended by FDA, and the result was (b) (4) mg/kg dw.

4. Physicochemical Properties and Environmental Fate

Bayer submitted physicochemical data of elinzanetant as summarized in the table below.

Physicochemical property	Test method	Result
Water solubility	OECD 105	1.55-12.3 mg/L (pH 4-9, 20 °C)
Dissociation constant (pK _a)	OECD 112	Not dissociated (pH 5-9, 20 °C)
Octanol/water partition coefficient (logK _{ow})	OECD 123	5.25-5.31 (pH 5-9, 25 °C)
Organic carbon-water partition coefficient (logK _{oc})	OECD 106	Soil (3 samples): 3.83-4.18 L/kg (pH 6.2-6.9, 20 °C) Sludge (2 samples): 3.76-3.95 L/kg (pH 5.8-6.5, 20 °C)
Vapor pressure	OECD 104	<8.4E-07 Pa (20 °C and 25 °C)

Bayer also conducted OECD tests on environmental fate of elinzanetant and the data are summarized in the table below.

Test	Method	Duration	Result
Hydrolysis	OECD 111	30 days	DT ₅₀ (25 °C): 196 days (pH 4); 112 days (pH 7); 59 days (pH 9)
Aerobic biodegradation	OECD 301F	28 days	Theoretical oxygen demand: 2-2.5%
Transformation in water-sediment	OECD 308	100 days	- Mineralization: <2% applied radioactivity (AR) - Remaining in the water phase: 2.8-6.8% AR - Remaining in extractable sediment: 51.4-63.6% AR - Remaining in non-extractable sediment (i.e., bound residues): 14.3-24.5% AR - DT₅₀ of elinzanetant (12 °C): 2.8-3.4 days (water phase); 86.8-141 days (water and extractable sediment)

According to the physicochemical data, Bayer stated that elinzanetant was not present in the atmosphere and could amass in the aquatic environment to some degree. Bayer also suggested that the fate and effect of elinzanetant in the terrestrial environment should be considered as the log K_{ow} and log K_{oc} data indicated that elinzanetant had a potential to adsorb to biosolids.

Based on the OECD 301F test results, Bayer considered elinzanetant not readily biodegradable. The OECD 308 test was conducted using ¹⁴C-labeled elinzanetant in two different water-sediment systems under aerobic conditions at 20°C in the dark. No evidence was found for abiotic degradation of elinzanetant. Of the remaining substances in the system (water and extractable sediment), most AR was attributed to the parent compound elinzanetant. A total of 11 transformation products were identified but considered minor as their abundances were below 5% AR, and thus no efforts were taken for further characterization. The DT₅₀ values derived in the water-sediment systems revealed slow biodegradation of elinzanetant over time.

Overall, Bayer concluded that elinzanetant was susceptible to hydrolysis and could undergo slow abiotic and biotic degradation in the environment.

5. Environmental Effects

Bayer conducted a series of ecotoxicity tests of elinzanetant, mostly chronic, in relevant organisms including microbes in activated sludge, aquatic organisms including algae,

aquatic invertebrate, fish, and sediment-dwelling midge, and terrestrial organisms including soil microbes, earthworm, and plants. Results including the no observed effect concentration (NOEC), bioconcentration factor (BCF), and EC₁₀ values are summarized in the table below.

Organism	Method	Duration	Endpoint	Result
Microbes in activate sludge	OECD 209	30 min	Respiration inhibition	NOEC ≥ (b) (4) ppm
Algae (<i>P. subcapitata</i>)	OECD 201	72 hours	Growth rate	NOEC ≥ (b) (4) ppb
Invertebrate (<i>D. magna</i>)	OECD 211	21 days	Survival, reproduction	NOEC = (b) (4) ppb
Zebrafish (<i>D. rerio</i>)	ZEOGRT	131 days	Survival, growth, reproduction	NOEC = (b) (4) ppb
Zebrafish (<i>D. rerio</i>)	OECD 305	15 days	Bioaccumulation	BCF = 62.9 L/kg
Midge (<i>C. riparius</i>)	OECD 218	28 days	Emergence, development	NOEC = (b) (4) ppm
Soil microbes	OECD 216	28 days	Inhibition of N transformation	NOEC ≥ (b) (4) mg/kg
Earthworm (<i>E. andrei</i>)	OECD 222	56 days	Mortality, weight, reproduction	NOEC ≥ (b) (4) mg/kg
Plants (<i>B. napus</i> , <i>B. oleracea</i> , <i>G. max</i> , <i>C. sativus</i> , <i>H. annuus</i> , <i>A. sativa</i> , <i>A. cepa</i>)	OECD 208	21 days	Emergence, fresh weight, mortality	NOEC = (b) (4) ppm; EC ₁₀ = (b) (4) mg/kg

Elinzanetant showed no effects on microbes in active sludge and algae up to the highest test concentrations of (b) (4) ppm and (b) (4) ppb, respectively. There was a toxic effect on reproduction of crustacean *D. magna* with a NOEC of (b) (4) ppb. Moderate toxicity in sediment organisms was observed in midge *C. riparius* with a NOEC of (b) (4) ppm. The study on bioaccumulation potential in fish indicated a low potential for bioaccumulation for elinzanetant. The lowest NOEC among the test aquatic organisms was determined to be (b) (4) ppb in zebrafish *D. rerio* from a ZEOGRT.

In the ZEOGRT with elinzanetant, which was performed using a multi-generation approach including the spawning period of the parental generation (F0), early life stages, juvenile growth, sexual maturation, and reproduction of the first filial generation (F1), and the early embryonal stage of the second filial generation (F2), adverse effects were observed on fish growth with NOECs of (b) (4) ppb in F0 and (b) (4) ppb in F1, and post-hatch survival with a NOEC of (b) (4) ppb in F1. For effects on fertility, significant reduced fertilization rates compared to the concurrent controls were observed in the treatment groups of F0 and F1 with concentrations ≥ (b) (4) ppb, suggesting the NOEC could be (b) (4) ppb. However, Bayer considered that the fertilization rate was not population relevant, as fertilization rates observed in the concurrent controls and all

treatment groups of F0 and F1 were well within the limits of historical control data (HCD) determined at the same test facility. In the IR responses, Bayer performed further assessment to revise and justify the HCD limits based on that the fertilization rate in the ZEOGRT with elinzanetant was considered not significant in causing negative effects on fish populations. No effects were observed for other endpoints up to the highest test concentration of (b) (4) ppb.

For terrestrial ecosystems, elinzanetant caused no effects in soil microorganisms and earthworms up to the highest test concentrations of (b) (4) mg/kg and (b) (4) mg/kg, respectively. Toxicity in terrestrial plants was observed in some test plants, resulting in a NOEC of (b) (4) mg/kg and an EC₁₀ of (b) (4) mg/kg.

6. Environmental Risk Assessment

Based on the above data of environmental effects and an assessment factor of 10, Bayer estimated the PNEC value of elinzanetant to be (b) (4) ppb for the aquatic environment and (b) (4) mg/kg for the terrestrial environment. They then calculated the risk quotient (RQ), which is the ratio of EIC to PNEC, as follows:

- $RQ \text{ (aquatic)} = \text{refined EIC (water)} / \text{PNEC (aquatic)} = (b) (4) \text{ ppb} / (b) (4) \text{ ppb} = (b) (4)$
- $RQ \text{ (terrestrial)} = \text{EIC (soil)} / \text{PNEC (terrestrial)} = (b) (4) \text{ mg/kg} / (b) (4) \text{ mg/kg} = (b) (4)$
- $\text{High-end RQ (terrestrial)} = \text{high-end EIC (soil)} / \text{PNEC (terrestrial)} = (b) (4) \text{ mg/kg} / (b) (4) \text{ mg/kg} = (b) (4)$

Since all these RQs were below 1, Bayer concluded that the EA revealed no risk from the use of elinzanetant in the aquatic or terrestrial environment, and no specific mitigation measures were required.

Bayer also conducted additional risk assessment to assess the potential ecological risks under various scenarios. Bayer used several approaches including the dilution factor of 1/10, E-FAST model, and iSTREEM model to estimate the expected environmental concentrations (EECs) of elinzanetant from down-the-drain release of elinzanetant to receiving riverine environments. The EECs estimated using the dilution factor and E-FAST model did not exceed the PNEC (aquatic) of (b) (4) ppb. The results of the iSTREEM model, which provides more refined estimates of the EEC than the other two approaches, showed that the predicted 95th percentile concentration of elinzanetant in continental U.S. rivers was (b) (4) ppb for the mean flow scenario and (b) (4) ppb for the low flow scenario, both of which are below the PNEC (aquatic) of (b) (4) ppb. Even using the “low-end” PNEC of (b) (4) ppb for risk assessment (i.e., disregarding the HCD limits

for the fertilization rate described in the previous section), the 95th percentile concentration under the mean flow scenario ((b) (4) ppb) was still below the low-end PNEC. Under the low flow scenario, however, the EECs would exceed the low-end PNEC of (b) (4) ppb in (b) (4) % of the U.S. rivers, which Bayer considered as the extreme exposure assumptions. Given that the modeled exposure estimates did not account for human metabolism or in-river decay and based on the assumption that all of the produced API was discharged down-the-drain in these model estimates, Bayer concluded that surface water risks were acceptable with a reasonable margin of safety.

Assessment: Adequate

Environmental Review:

The main goals of the environmental review, per 21 CFR 25.15(a) and (b), and 25.40, are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment; and (2) if so, whether the proposed action will significantly affect the environment. Regarding the main findings of the original EA as well as the additional information that Bayer submitted in their IR responses:

- Bayer described the API elinzanetant and excipients, noting elinzanetant as the substance of interest. This is appropriate based on FDA 1998 guidance [2], which notes that the EA should focus on the active moiety and the predominant structurally related substances expected to enter or exist in the environment.
- The estimated EIC values of elinzanetant in the aquatic and terrestrial environments are acceptable. FDA independently developed an estimate of the production of elinzanetant, which was similar to Bayer's estimate. FDA agrees with Bayer's calculated EIC (water) of (b) (4) ppb. Bayer further predicted the emission rate of elinzanetant in WWTP effluent to be (b) (4) % and used this estimate to refine the EIC (water). Considering the high $\log K_{ow}$ of elinzanetant (>5), which suggests that elinzanetant is highly hydrophobic and can be substantially bound to sludge, and FDA's own estimate of elinzanetant residue in WWTP effluent ((b) (4) %) using EPA's EPI Suite model, FDA agrees with Bayer's predicted emission rate of (b) (4) % for elinzanetant. No other refinement from human metabolism was considered as no evidence showing the metabolites of elinzanetant have less pharmacological activities than the parent compound. Therefore, FDA considers this refinement approach as reasonable for a conservative risk assessment and agrees with the refined EIC (water) of (b) (4) ppb. For the terrestrial environment, FDA considers that the calculated EIC (soil) of (b) (4) mg/kg dw and the high-end EIC (soil) of (b) (4) mg/kg dw

are highly conservative as Bayer didn't consider the potential distribution of elinzanetant to sludge, which can be significant based on its physicochemical properties and the predicted partition of (b) (4) % to sludge by the SimpleTreat model.

- The submitted physicochemical data of elinzanetant are acceptable. FDA agrees that the water and terrestrial compartments need assessment, and the air compartment assessment is not needed. Elinzanetant is expected to have a strong adsorption to activated sludge during the wastewater treatment process, and is slightly/hardly mobile in soil. Based on its chemical structure, elinzanetant is susceptible to hydrolysis in basic environment as proven by its decreasing DT₅₀ with an increasing pH; yet it is relatively stable at environmentally relevant pH 7.0. According to the OECD 308 test results, FDA considers that elinzanetant is potentially persistent in the natural aquatic environment as it is not readily biodegradable, has slow biotransformation rate, and has relatively long DT₅₀ of 86.8-141 days in the water-sediment systems (water and extractable sediment). Once emitted to the aquatic environment, elinzanetant is expected to be rapidly distributed from the water phase to sediment. About 14-25% of the introduced elinzanetant may form non-extractable bound residues in sediment, and about 50% may exist in the extractable fraction of sediment, mostly as the parent compound, which is considered still bioaccessible and bioavailable and could be released back to the water phase under certain environmental conditions.
- The ecotoxicity studies and toxicity values of elinzanetant provided by Bayer are acceptable. FDA agrees that elinzanetant shows low to moderate toxicity in the test aquatic and terrestrial organisms except fish. It has low potential for bioconcentration in aquatic organisms and thus its risk to animals higher in the aquatic food chain is expected to be negligible. As expected, fish is the most sensitive organism to elinzanetant which has endocrine-related activity. FDA acknowledges Bayer's argument of using the HCD to determine whether the fertilization rate may be a biological/toxicological relevant effect for ZEOGRT with elinzanetant. FDA also recognizes, however, that this HCD approach is still controversial and yet to be harmonized [5,6]. After careful review and assessment, FDA considers that Bayer's revised HCD limits for fertilization rate following the approaches recommended by Kluxen et al. [7] are acceptable. All treatment-related responses in fertilization rate were fully within the HCD limits, suggesting that the dose-response is so weak that it cannot be distinguished from biologically plausible responses [7]. Accordingly, FDA agrees with Bayer's justification for applying the HCD to determine that the fertilization rate is not a population relevant toxicity endpoint in the ZEOGRT with elinzanetant, and their conclusion of the NOEC of (b) (4) ppb for fish.

- The environmental risk assessments of elinzanetant in the aquatic and terrestrial environments are acceptable. FDA agrees with Bayer that elinzanetant doesn't seem to have adverse environmental effects at the expected levels of exposure, as the RQs in the aquatic and terrestrial environments are below the threshold value of 1. FDA also considers that Bayer's further prediction of the EECs and potential risks using three different approaches are acceptable, although their extreme exposure assumptions seem unrealistic for a long-term/chronic effects assessment scenario, as the low flow data are from the lowest seven consecutive days of flow over a 10-year period. Considering the environmental depletion mechanisms, e.g., distribution and forming non-extractable bound residues in sediment (14-25% for elinzanetant according to OECD 308 test), the actual concentrations of elinzanetant in the aquatic environment are expected to be lower than the predicted concentrations in this EA, which may further reduce the RQ (aquatic) as well as the ecological risk. Thus, the adverse effects, if there are any, are unlikely to be significant.

Overall Assessment and Recommendation:

Overall, the submitted information for environmental assessment of elinzanetant is sufficient to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment.

FDA concludes that no significant environmental effects are expected from the approval of NDA 219469 ORIG-1. Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

References

1. U.S. FDA, 2016. Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity. Center for Drug Evaluation and Research. <https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf>
2. U.S. FDA, 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications>
3. EMA, 2024. Guideline on the environmental risk assessment of medicinal products for human use. <https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use-scientific-guideline>

4. U.S. EPA, 2000. Biosolids Technology Fact Sheet, Land Application of Biosolids.
<https://www.epa.gov/sites/default/files/2018-11/documents/land-application-biosolids-factsheet.pdf>
5. EFSA Panel on Plant Protection Products and their Residues, 2024. Draft scientific opinion on the use and reporting of historical control data for regulatory studies.
<https://connect.efsa.europa.eu/RM/s/consultations/publicconsultation2/a0ITk000000Cvs9IAC/pc0856>
6. Zarn et al., 2024. Letter to the Editors regarding “Using historical control data in bioassays for regulatory toxicology” by Kluxen et al. (2021). Regulatory Toxicology and Pharmacology, 149, 105624.
7. Kluxen et al., 2021. Using historical control data in bioassays for regulatory toxicology. Regulatory Toxicology and Pharmacology, 125, 105024.

Primary Environmental Assessor Name and Date: Xiaoqin Wu, 3/17/2025

Secondary Assessor Name and Date: James P. Laurenson, 3/21/2025



James
Laurenson

Digitally signed by James Laurenson

Date: 3/21/2025 02:50:48PM

GUID: 51dc6bdb0000c62de59b85452e59746f



Xiaoqin
Wu

Digitally signed by Xiaoqin Wu

Date: 3/21/2025 01:20:51PM

GUID: 625df66f00cc22833bedee13222a2cba

Finding of No Significant Impact

**NDA 219469 ORIG-1 Elinzanetant
60 mg capsule, two capsules once daily**

**Food and Drug Administration
Center for Drug Evaluation and Research**

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental effects of approving certain drug product applications and supplements to such applications as an integral part of its regulatory process.

Bayer HealthCare Pharmaceuticals Inc. requests approval of the original NDA 219469 for the drug product elinzanetant (60 mg capsule) for the treatment of moderate to severe vasomotor symptoms associated with menopause. The active pharmaceutical ingredient (API) is elinzanetant, which is a non-hormonal, selective neurokinin 1 (NK-1) and 3 (NK-3) receptor antagonist that blocks NK-1 and NK-3 receptors signaling on kisspeptin/neurokinin B/dynorphin neurons.

In support of the application, Bayer submitted an environmental assessment (EA) for elinzanetant (attached), which evaluated the potential environmental effects from the use of this drug product. The FDA Center for Drug Evaluation and Research (CDER) EA Team reviewed and assessed the original EA as well as Bayer's subsequent responses to FDA's information requests, and carefully considered the potential adverse effects due to approval of this drug product application. While FDA does not agree with some of the final results, FDA concludes that the submitted information is sufficient to enable the Agency to determine whether approval of this application may significantly affect the quality of human environment, and thus the EA is adequate for approval, per 21 CFR 25.15(a).

Based on the review and assessment of the entirety of submitted information, FDA has determined that approval of this NDA is not expected to have a significant effect on the environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and an environmental impact statement will not be prepared, per 21 CFR 25.15(b), 25.40, and 25.41.

Attachment: Environmental Assessment for Elinzanetant (original version)



Environmental Assessment (EA)

Elinzanetant

02 July 2024

Head of Ecotoxicology (author):

Date, (b) (4)

Head of Industrial Chemicals &
Marketed Products Toxicology:

Date, (b) (4)

(b) (4)

Table of Contents

Definitions	4
1. Date.....	6
2. Name of Applicant.....	6
3. Address.....	6
4. Description of Proposed Action	6
5. Identification of Substances that are Subject of the Proposed Action	7
6. Environmental Issues.....	8
6.1 Assessing Toxicity to Environmental Organisms.....	8
6.2 Regulatory interactions pertaining to the EA of elinzanetant.....	10
6.3 Identification of Substance of Interest	11
6.4 Physico-Chemical Characterization.....	12
6.4.1 Conclusion on distribution in environmental compartments.....	13
6.5 Environmental depletion mechanisms	14
6.5.1 Conclusion on Environmental Depletion	16
6.6 Environmental Concentrations	16
6.6.1 Expected Introduction Concentration in Aquatic Systems (EIC _{aquatic}).....	16
6.6.2 EEC- Expected Environmental Concentration	17
6.6.3 Expected Introduction Concentration in Terrestrial Systems (EIC _{terrestrial})	18
6.6.4 Conclusions on environmental concentrations (EIC).....	18
6.7 Read-across analysis to inform need of terrestrial assessment	19
6.7.1 Conclusion on the Need of a Terrestrial Assessment.....	19
6.8 Environmental Effects	19
6.8.1 Results of Microbial Inhibition Test.....	20
6.8.2 Results of Aquatic Ecotoxicity Studies	20
6.8.3 Additional Ecotoxicological Data	23
6.8.4 Results of Terrestrial Ecotoxicity Studies	24
6.9 Risk assessment	26
6.9.1 Surface water risk assessment	26
6.9.2 Terrestrial compartment	26
6.10 Summary of environmental effects tests.....	27
7. Mitigation measures.....	27
8. Alternatives to the Proposed Action	28
9. List of Preparers.....	29
9.1 Curriculum Vitae of the Preparer.....	29
10. References	30
10.1 Literature.....	30
10.2 Reports	32
11. Appendix A - Nonconfidential Data	34
12. Appendix B - Confidential Data.....	35
13. Appendix C – SimpleTreat Calculation	36

List of Tables

Table 5–1: Identification elinzanetant.....	7
Table 6–1: Environmental Fate and Effects Studies Completed for the EA for elinzanetant....	9
Table 6–2: Regulatory interactions pertaining to the EA of elinzanetant.....	10
Table 6–3: Physico-chemical properties	13
Table 6–4: Mass balance of ¹⁴ C radio-labelled substance in the water-sediment transformation study after 100 days [% of initially introduced radioactivity].....	15
Table 6–5: Recalculation of half-lives (DT ₅₀) from 20 °C (test condition) to 12 °C (standard temperature).....	16
Table 6–6: Depletion data	16
Table 6–7: Parameters used to calculate EIC _{aquatic}	17
Table 6–8: Elinzanetant (active moiety) usage based on projected sale volumes of elinzanetant in the USA	17
Table 6–9: Parameters used to calculate EIC _{terrestrial}	18
Table 6–10: Microbial inhibition test.....	20
Table 6–11: Aquatic Ecotoxicity studies	23
Table 6–12: Additional Aquatic Ecotoxicity Studies.....	23
Table 6–13: Terrestrial toxicity studies.....	26

Definitions

AF	Assessment factor
API	Active Pharmaceutical Ingredient
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
DF	Depletion factor
DT50	Degradation half-life of substance (in a given compartment)
EA	Environmental Assessment
EAS	Endocrine active substance
EC10	Effect concentration at which 10 % effect (mortality, inhibition of growth, reproduction, etc) is observed compared to the control group
EC50	Effect concentration at which 50 % effect (mortality, inhibition of growth, reproduction, etc) is observed compared to the control group
ErC10	Effect concentration at which 10 % effect for inhibition of growth rate is observed compared to the control group
ECHA	European Chemicals Agency
GLP	Good Laboratory Practice
GnRH	Gonadotropin Releasing Hormone
HMP	Human medicinal product
HPG	Hypothalamic-Pituitary-Gonadal axis
KFOC	Organic carbon normalised adsorption partition coefficient
Kow	Octanol/water partition coefficient
log D _{ow}	Logarithm of octanol/water distribution coefficient for ionisable compounds
log K _{ow}	Logarithm of octanol/water partition coefficient
MoA	Mode of action ((eco)toxicological)
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MF	Metabolism Factor
NDA	New Drug Application
NER	Non-extractable residues
NOEC	No observed effect concentration
NOErC	No observed effect concentration for growth rate
OC	Organic carbon
OECD	Organisation for Economic Co-operation and Development
PEC	Predicted environmental concentration (in a given compartment)
pK _a	Dissociation constant
PL	Package leaflet
PNEC	Predicted No Effect Concentration
PBT	Persistent, Bioaccumulative and Toxic (substance classification)



QSAR	Quantitative structure–activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RQ	Risk Quotient (for a given compartment)
STP	Sewage treatment plant
VMS	Vasomotor Symptoms



1. Date

02 July 2024

2. Name of Applicant

Bayer HealthCare Pharmaceuticals Inc.

3. Address

The address of the applicant is

Bayer HealthCare Pharmaceuticals Inc.,

100 Bayer Blvd.,

P.O. Box 915,

Whippany, NJ 07981-0915, USA.

4. Description of Proposed Action

a.) Requested Action

Bayer Healthcare Pharmaceuticals Inc. is filing an NDA 219469 pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for elinzanetant for the treatment of moderate to severe vasomotor symptoms associated with menopause. Elinzanetant is available as 60 mg soft gelatin capsules and the therapeutic dose of 120 mg will be delivered using two soft gelatin capsules taken once-a-day before bedtime. Soft gelatin capsules are packaged in blister card; each card containing 12 capsules and 5 blister cards are packaged in a carton that provides 60 capsules for one-month supply.

Pursuant to 21 CFR Part 25 Bayer has prepared an environmental assessment (EA) for elinzanetant in accordance with FDA Guidance's. While the calculated Environmental Introductory Concentration (EIC) in the aquatic compartment is below 1 ppb, the requirement of extraordinary circumstances could not be excluded due to potential endocrine related activity. A comprehensive plan including completed, ongoing and planned studies was discussed with the FDA in a Type D Meeting on 14 November 2023. As agreed in the Type D meeting, Bayer has conducted a series of studies to assess the environmental impact of elinzanetant that form the basis of the EA being submitted along with the NDA. Considering the calculated EIC (< 1 ppb) and the risk quotients of less than 1 in both the aquatic and terrestrial environments, Bayer considers that the approval of elinzanetant by FDA will not significantly affect the quality of environment and thus the issuance of finding of no significant impact (FONSI) will be feasible under 21 CFR§25.40.

b.) Need for Action

Elinzanetant will be used as a prescription medication in women for the treatment of moderate to severe vasomotor symptoms associated with menopause.

c.) Location of Use

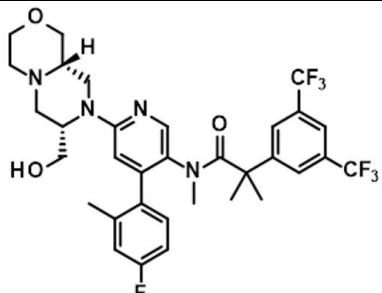
Elinzanetant will be self-administered by patients in their homes. The proposed distribution of the product is to be dispensed from a retail or hospital pharmacy setting.

d.) Disposal Site

No special method of disposal of waste by the end user is anticipated. In the home, empty or partially empty packaging, i.e., blisters will often be disposed of by community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of unused drug could be disposed of in the sewer system. The hospitals, pharmacies or clinics will dispose of empty or partially emptied packages in accordance with applicable local, state, and federal regulations.

5. Identification of Substances that are Subject of the Proposed Action

Table 5–1: Identification elinzanetant

INN / USAN	Elinzanetant
Company code	BAY 3427080
Proprietary Name	LYNKUET (conditionally acceptable by FDA)
IUPAC name	2-[3,5-bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]pyridin-3-yl}-N,2-dimethylpropanamide
CAS number	929046-33-3
Molecular formula	C ₃₃ H ₃₅ F ₇ N ₄ O ₃
Structural formula	
SMILES	CC1=C(C=CC(=C1)F)C2=CC(=NC=C2N(C)C(=O)C(C)(C)C3=CC(=C(C=C3)C(F)(F)F)C(F)(F)F)N4CC5COCCN5CC4CO
Molecular mass	668.7 g/mol (free base)

Drug Product

Elinzanetant will be available as a 60 mg soft capsule. The list of excipients used in the manufacture of the capsule is provided below. No novel excipients are used in the manufacture of elinzanetant.

Capsule fill

All-rac- α -Tocopherol
 Caprylocaproyl macrogolglycerides
 Glycerol monocaprylocaprate
 Glycerol mono-oleate
 Polysorbate 80

Capsule shell
Ferric oxide red
Ferric oxide yellow
Gelatin
Sorbitol special–glycerin blend
Titanium dioxide
Printing ink
Ammonia solution, concentrated
Isopropyl alcohol
Macrogol 400
Polyvinyl acetate phthalate
Propylene glycol
Purified water
SDA 35A alcohol
Titanium dioxide

6. Environmental Issues

6.1 Assessing Toxicity to Environmental Organisms

In accordance with the FDA guidance (1), Bayer has evaluated the environmental impact of elinzanetant to support its NDA 219469. Per the guidance, a categorical exclusion (CE) is feasible if the expected introduction concentration (EIC) of the substance at the point of entry into the aquatic environment is less than 1 parts per billion (ppb) and no extraordinary circumstances exist. Based upon marketing expectations, the worst-case concentration of elinzanetant at the point of entry into the aquatic environment (EIC_{aquatic}) is (b) (4) ppb and the refined concentration ($EIC_{\text{aquatic_refined}}$) is calculated to be (b) (4) ppb. Since each EIC is below the threshold of 1 ppb, an EA would not be required if no extraordinary circumstances exist. However, with respect to elinzanetant the absence of extraordinary circumstances cannot be excluded with certainty because the nonclinical and clinical data suggest that elinzanetant may have potential endocrine related activity. Therefore, additional assessment was initiated in line with the FDA 2016 guidance (2).

Elinzanetant is a non-hormonal, selective neurokinin 1 (NK-1) and 3 (NK-3) receptor antagonist that blocks NK-1 and NK-3 receptors signaling on kisspeptin/neurokinin B/dynorphin (KNDy) neurons to modulate neuronal activity involved in thermo- and sleep regulation. KNDy neurons in the hypothalamus are hyperactivated due to estrogen decline in menopause. NK-3 receptor signaling is known to biologically play a role in the modulation of the hypothalamic-pituitary-gonadal (HPG) axis by modulating the Gonadotropin Releasing Hormone (GnRH) pulse generator (7)(11). Moreover, NK-1 and NK-3 receptors are present in other species including fish (10)(8)(12) and a potential role of these receptors in the reproductive axis in fish is postulated (6). A knock-out of the 2 *tac3* genes (proposed ligands for NK-3 receptor) in zebrafish (*Danio rerio*) did not impair reproductive functions, demonstrating the plasticity of the reproductive neuroendocrine system in the brain of zebrafish (9). However, it cannot be completely ruled out that signaling via NK receptors is involved in the reproductive axis in fish.

The main objective of this EA is to assess the potential endocrine related effects of elinzanetant in the environment. The EA for elinzanetant was developed in a scientifically directed manner in accordance with FDA guidance documents (1)(2) and the advice received from FDA in the Type D Meeting (Type D Briefing Package and FDA responses, 2023). A summary of the studies for the systematic evaluation is provided in Table 6–1 with links to the study reports that are further described in the subsequent sections.

Table 6–1: Environmental Fate and Effects Studies Completed for the EA for elinzanetant

Test method	Guideline	Status in EA	Study Number	Report Number
Physico-Chemical Characterization Studies				
Water Solubility	OECD 105	Final Report	T105486-4	R-14369
Dissociation constant	OECD 112	Final Report	T105488-6	B002189
Partition coefficient	OECD 123	Final Report	T105487-5	B002064
Adsorption-Desorption behavior	OECD 106	Final Report	T105492-1	R-14250
Vapor Pressure	OECD 104	Final Report	T105485-3	R-14295
Hydrolysis	OECD 111	Final Report	T105491-0	R-14426
Environmental Fate Characterization Studies				
Aerobic biodegradation (Ready biodegradability study)	OECD 301F	Final Report	T105486-7	R-14371
Transformation water-sediment	OECD 308	Final Report	T105493-2	B002870
Bioaccumulation	OECD 305	Final Report	T105787-8	B003370
Ecotoxicological Studies				
Algae Growth Inhibition Test	OECD 201	Final Report	T105494-3	B002234
Daphnia magna Reproduction Test	OECD 211	Final Report	T105495-4	B002235

Table 6–1: Environmental Fate and Effects Studies Completed for the EA for elinzanetant

Test method	Guideline	Status in EA	Study Number	Report Number
Respiration Inhibition	OECD 209	Final Report	T105497-6	B002708
Sediment-water Chironomid study	OECD 218	Final Report	T105994-8	B003366
Zebrafish Extended One-Generation Reproduction Toxicity (ZEOGRT) study	OECD test guideline on EOGRT study with zebrafish	Final Report	T105668-6	B003372
Soil micro-organisms	OECD 216	Final Report	T105969-0	B003102
Earthworm reproduction	OECD 222	Final Report	T105970-2	B003351
Seedling emergence	OECD 208	Final Report	T105971-3	B003379
Additional Studies				
Read-across analysis for terrestrial studies with elinzanetant	-	Final Report	-	T106131-2
Elinzanetant: Biotransformation in Man	-	Final Report	-	PH-42275

6.2 Regulatory interactions pertaining to the EA of elinzanetant

Table 6–2: Regulatory interactions pertaining to the EA of elinzanetant

Type of Correspondence	IND 129492 eCTD Sequence/Date	Interaction/Correspondence
Type D Briefing Book	0112 06 Oct 2023	Bayer submitted Type D Meeting Package to seek Agency's feedback on the EA of elinzanetant.

Preliminary Response from FDA	14 Nov 2023	Agency's preliminary comments were received. The key feedback included: - to consider Risk Quotient (RQ) approach for the EA - perform read-across analysis to assess the need for terrestrial studies - submit a preliminary EA prior to NDA In response to the Agency's comments, Bayer agreed to perform the read-across analysis as well as calculate RQ. Bayer further indicated that submission of preliminary EA will not be feasible due to the timing of the data availability.
Meeting Cancelled Letter from FDA and Advice Letter	20 Nov 2023 30 Nov 2023	While the actual meeting was cancelled, the preliminary responses and Bayer's responses were considered final. However, Agency issued a separate Advice Letter indicating the agreement to accept following documents as late components to the NDA - Final study report for ZEOGRT study during the 60-days filing review period. - Terrestrial studies, if needed during the NDA review

6.3 Identification of Substance of Interest

After oral administration and absorption from the intestine, elinzanetant is predominantly eliminated from plasma by hepatic metabolism. The major route of excretion of drug-related material is via feces, mainly as metabolites. In a human mass balance study LC-MS analytics were used to determine elinzanetant (parent compound) and metabolites by comparison against total radioactivity (see M4.2.2.4; report No. [PH-42275](#)). Elinzanetant covered 39.1 % of total radioactivity in the AUC(0-144) plasma pool. Metabolites M30/M34, M27 and M18/M21 accounted for 13.7 %, 7.6 % and 4.9 % of total radioactivity AUC(0-144), respectively. All other identified metabolites covered in sum 14.3 % of total radioactivity AUC(0-144) (each less than 3.5 %). Elinzanetant is degraded into M27 and M18/21 and both are further degraded into M30/34. In total, these four analytes (elinzanetant and the three principal metabolites) accounted for about 53 % of circulating plasma total radioactivity. Consequently, metabolite M30/M34 with greater than 10 % of total radioactivity AUC(0-144) is considered a principal metabolite. The majority of administered radioactivity (AR) was excreted in feces amounting to 88-91 %, while only 0.22-0.85 % was excreted in urine (Module 2.7.2 Section 3.1.4). All three metabolites exhibit a similar pharmacological activity compared to the parent compound. The activity of minor metabolites is unknown. Since unchanged elinzanetant and the three metabolites possess similar pharmacological activity,

the EA of elinzanetant considers the total residue approach according to the FDA guidance (1).

6.4 Physico-Chemical Characterization

Studies on physico-chemical properties are summarized below and key results are compiled in Table 6–3. All studies were conducted in accordance with OECD test methods and GLP requirements.

Water Solubility

Water solubility of elinzanetant was determined in an OECD 105 study with the column elution method at pH 4, 5, 7 and 9 (report No. R-14369). The saturation mass concentrations of the test item were determined using LC-MS/MS. The solubility between pH 5 to 9 was constant with 1.7 mg/L at pH 7. The water solubility at pH 4 was 12.3 mg/L.

Vapor Pressure

The vapor pressure was determined in an OECD 104 study (report No. R-14295). The isothermal thermogravimetric effusion method was applied, and data were generated between 200 °C and 215 °C. The vapor pressure was below the calibrated range of 8.4×10^{-7} Pa to 2.3×10^3 Pa. The extrapolated vapor pressure was calculated as 7.33×10^{-13} Pa at 20 °C and 2.6×10^{-12} Pa at 25 °C, both below the lower threshold of 10^{-10} Pa that can be measured with that test method. The vapor pressure of elinzanetant was therefore reported at the experimental limit value (lower calibration range) as $<8.4 \times 10^{-7}$ Pa at 20°C and 25 °C, respectively.

Partition Coefficient

The partition coefficient was determined according to OECD test method 123, using the slow stirring method (report No. B002064). LC-MS/MS analysis was applied. All validity criteria were met. The log P_{OW} was calculated for each sampling separately.

According to this study, the logarithmic *n*-octanol/water partition coefficient (log K_{OW}) of the test item was constant between pH 5 to 9 with 5.31 at pH 7.

Adsorption Coefficient

In a study conducted in accordance with OECD 106 the adsorption/desorption behavior of elinzanetant was evaluated in 3 soils and 2 sewage sludges (report No. R-14250). All validity criteria were met. While some degradation was observed, the test item was sufficiently stable over the study period. Furthermore, adsorption of the test item to the inner surface of the test vessels was observed, which could not be prevented but is not considered to affect the result. The adsorption coefficient (K_{OC}) ranged between 6,804-14,986 for the soils and 5,734-8,820 for the sludges. The Freundlich coefficient K_{FOC} ranged between 3,653-12,897 for the soils and between 5,388-6,633 for the sludges.

Dissociation Constant

The dissociation constant was assessed in an OECD 112 study applying the spectroscopic method (report No. [B002189](#)). At 20 °C and in the pH range from 1 to 13 no dissociation of elinzanetant was observed.

Table 6–3: Physico-chemical properties

Parameter	Results	Method	Report No.
Water solubility	12.3 mg/L (pH 4) 2.97 mg/L (pH 5) 1.70 mg/L (pH 7) 1.55 mg/L (pH 9) (20 °C)	OECD 105	R-14369
Vapor pressure	< 8.4x10 ⁻⁷ Pa (20 °C and 25 °C)	OECD 104	R-14295
<i>n</i> -octanol:water partition coefficient	Log K _{OW} = 5.25 (pH 5) K _{OW} = 177,828 (pH 5) Log K _{OW} = 5.31 (pH 7) K _{OW} = 204,174 (pH 7) Log K _{OW} = 5.28 (pH 9) K _{OW} = 190,546 (pH 9) (25 °C)	OECD 123	B002064
Adsorption coefficient	Soil Log K _{OC} = 3.83-4.18 K _{OC} = 6,804-14,986 Log K _{F,OC} = 3.56-4.11 K _{F,OC} = 3,653-12,897 (20 °C, pH = 6.2-6.9) Sludge Log K _{OC} = 3.76-3.95 K _{OC} = 5,734-8,820 Log K _{F,OC} = 2.73-3.82 K _{F,OC} = 5,388-6,633 (20 °C, pH = 5.8-6.5)	OECD 106	R-14250
Dissociation constant	pK _a = none, not dissociated (20 °C; pH 5, 7, and 9)	OECD 112	B002189

6.4.1 Conclusion on distribution in environmental compartments

Physico-chemical data was used to inform whether elinzanetant has potential to amass predominantly in aquatic, terrestrial, and/or atmospheric environments. Considering the very low vapor pressure, elinzanetant is non-volatile and is not expected to be present in the atmosphere.

The physico-chemical data suggests amassing in the aquatic environment to some degree. However, based on the FDA guidance (FDA 1998), compounds with a log K_{OW} > 3.5 should be further analyzed for the sorption and/or desorption properties of a substance (K_{OC}) to biosolids. Given that the partition coefficient (log K_{OW} of 5.31) of elinzanetant exceeds the threshold of 3.5, its sorption and/or desorption property (K_{OC}) was assessed. The adsorption coefficient (K_{OC}) ranged between 5,388-6,633 for sludge and 3,653-12,897 for soil. Each of these values exceeds the threshold of ≥ 1,000 specified in the FDA guidance, suggesting that

elinzanetant has potential to adsorb to biosolids. Therefore, fate and effect testing in the terrestrial environment should be considered.

6.5 Environmental depletion mechanisms

Depletion mechanisms were assessed in experimental studies in accordance with OECD test methods and GLP requirements.

Hydrolysis

The rate of hydrolysis of elinzanetant was assessed according to test method OECD 111 (report No. [R-14426](#)). Hydrolysis was assessed at pH 4, 7, and 9 for 30 days. There was a rapid concentration decrease at the first sampling point at low temperature of 18 °C, which was less pronounced at two higher temperatures of 50 °C and 60 °C. The initial rapid decrease at low temperature was attributed to initial adsorption to the glass in parallel to hydrolysis. This prevented the use of single-first-order (SFO) kinetic, and the evaluation was therefore based on hockey-stick (HS) kinetic. At pH 4 and pH 7, the last sampling points after 30 days at 60 °C were excluded from the evaluation. These data points deviated significantly from the typical course of hydrolysis due to a sudden decrease in concentration, for which neither a technical nor a scientific explanation could be found. The exclusion of these datapoints resulted however in higher hydrolysis half-lives (DT_{50}). The DT_{50} at 25 °C were calculated to be 196, 112, and 59 days at pH 4, 7, and 9, respectively.

Ready biodegradation

Ready biodegradability of elinzanetant was determined in a screening study in accordance with OECD 301F (report No. [R-14371](#)). There were no deviations from the study plan and all validity criteria were met. Aerobic activated municipal sewage sludge was exposed to 104.1 mg/L test item for 28 days. The reference item sodium benzoate was degraded by 85 % after 14 days (and to 91 % after 28 days). Due to the nitrogen moieties of elinzanetant, degradation percentages were calculated as Theoretical Oxygen Demand ($ThOD_{NO_3}$ and $ThOD_{NH_4}$). The toxicity control with sodium benzoate and the test item showed 36 % and 40 % biodegradation after 14 days and 39 % and 43 % after 28 days based on $ThOD_{NO_3}$ and $ThOD_{NH_4}$, respectively. Therefore, no toxicity of elinzanetant to the microbial community was observed. Elinzanetant never reached 10 % biodegradation over the incubation period. The mean biodegradation after 28 days was 2 % ($ThOD_{NO_3}$) and 2.5 % ($ThOD_{NH_4}$). Elinzanetant is therefore considered not readily biodegradable.

Water-sediment transformation study

Biodegradation was further assessed in a study conducted in accordance with the OECD test method 308 (report No. [B002870](#)). This study investigated the degradation and transformation of [^{14}C] BAY 3427080 in two different sediment systems under aerobic conditions at 20°C in the dark. The transformation rate and degradation pathway were assessed in both sediment systems using a treatment rate of 0.2 mg/L.

For liquid scintillation counting (LSC) and high-pressure liquid chromatography (HPLC) analysis, the limit of detection (LOD) was 0.7 % of the applied radioactivity (AR) (water phase and sediment extract) and 0.8 % AR (water phase) or 1.3 % AR (sediment extract), respectively. Thus, the sensitivity of both analytical methods was considered acceptable, as the detection of major transformation products could be performed down to 5 % AR. Column recovery was determined to investigate the total elution of the injected radioactivity (HPLC).

Values between 101.5 % and 114 % of the injected radioactivity were found and thus the analytical method was considered acceptable to analyze the obtained samples.

The results reported in the text below represent both sediments assessed and give the range or the mean. Results specific to each sediment and based on LSC measurement are provided in [Table 6–4](#).

The mass balances were in the range of 73.7-108.6 % AR for both sediments. Most of the values were below the required range of 90-110 % AR. Efforts to increase the recovery such as additional vessel wash and rinsing of the used equipment with different solvents, additional trapping material (Tenax) did not improve the recovery. Using sterile processing of samples, the overall mass balance was improved to 87.8 % AR. These results indicate no evidence for abiotic degradation of the test item.

In addition, since no significant amounts of volatiles or $^{14}\text{CO}_2$ were detected during the study the losses of test item were attributed to the high adsorptive properties of the test item and losses may be attributed to irreversible adsorption to test vessels and sampling equipment.

The maximum formation of non-extractable residues (NER) was 22.5 % AR. Mineralization to CO_2 as well as formation of volatile organic compounds (VOCs) was negligible (the amount never exceeded 1.8 % AR in both sediments).

For the test item a clear degradation was observed in both sediment systems over the study period. In the water phase of both sediment systems, the amount of test item decreased until the end of the test. At test start, 102.5 % AR (sediment A) and 95.1 % AR (sediment B) were found, and at the end of the test the amounts were below the LOD (sediment A) and 3.8 % AR (sediment B).

The extractable amount from the sediment phase was 6.1 % AR (sediment A) and 10.6 % AR (Sediment B) at test start. It increased to a maximum of 55.9 % AR at day 7 (sediment A) or 55.5 % AR at day 28 (sediment B). After day 100 (test end) the amounts were 48.9 % AR (sediment A) and 48.3 % AR (sediment B).

For the total system, a decrease of the amounts of the test item was observed. In sediment system A, it decreased from 108.6 % AR at test start to 48.9 % AR at the end of the test, and in sediment B from 105.6 % AR at test start to 52.2 % AR at the end of the test.

Screening for transformation products revealed 11 signals. All signals were considered minor transformation products as they were below 5 % AR at any time over the study period and thus no efforts were made for further characterization.

Table 6–4: Mass balance of ^{14}C radio-labelled substance in the water-sediment transformation study after 100 days [% of initially introduced radioactivity]

Parameter	Sediment A	Sediment B
Total mass balance	73.7-108.6	82.6-105.6
Recovery in water	2.8-2.9	5.3-6.8
Recovery in sediment	51.4-55.8	56.3-63.6
VOC	0.02-0.14	0.01-0.04
Trapped as $^{14}\text{CO}_2$	1.1-1.8	0.7
Sediment non-extractables (NER)	20.4-24.5	14.3-17.3

In conclusion, [^{14}C] elinzanetant was found to be degraded slowly in both sediment systems during an incubation period of 100 days. DT_{50} values were determined based on the best fitting kinetic, either first-order multi-compartment (FOMC), single first-order (SFO) or dual first-order in parallel (DFOP).

Half-lives were determined in that study at 20 °C test temperature and these were recalculated for 12 °C (Table 6–5). Total system DT₅₀ ranged from 86.8 to 141 days.

Table 6–5: Recalculation of half-lives (DT₅₀) from 20 °C (test condition) to 12 °C (standard temperature)

Temperature (°C)	Half-live (days)	Sediment A			Sediment B		
		water	sediment	total	water	sediment	total
20	DT ₅₀	1.33	543	66.3	1.60	10,000	40.9
12		2.82	1153	141	3.40	21,230	86.8

6.5.1 Conclusion on Environmental Depletion

The environmental depletion of elinzanetant was assessed using the following three studies: Hydrolysis, ready biodegradation, and transformation in a water-sediment system. Key results of the depletion studies are summarized in Table 6–6.

Table 6–6: Depletion data

Study	Results	Method	Report No.
Hydrolysis	DT ₅₀ = 196 (pH 4) DT ₅₀ = 112 (pH 7) DT ₅₀ = 59 (pH 9) (25 °C)	OECD 111	R-14426
Ready biodegradability	2-2.5 % in 28 d	OECD 301F	R-14371
Water sediment transformation	DT ₅₀ (water, aerobic) = 2.82-3.40 days DT ₅₀ (sediment / total system, aerobic) = 86.83-140.75 days	OECD 308	B002870

Elinzanetant was found to be slowly degrading and susceptible to hydrolysis. While insignificant biodegradation was observed in the ready biodegradability test, half-lives derived in the water-sediment system in a transformation study revealed slow degradation over time.

In conclusion, the environmental depletion data indicate that elinzanetant is susceptible to slow abiotic and biotic degradation in the environment.

6.6 Environmental Concentrations

6.6.1 Expected Introduction Concentration in Aquatic Systems (EIC_{aquatic})

(b) (4)

6.7 Read-across analysis to inform need of terrestrial assessment

In the Type D meeting preliminary responses of 14 November 2023, the Agency recommended to conduct a read-across analysis to further assess if terrestrial studies would be needed. Therefore, a read-across analysis based on the OECD QSAR Toolbox in the most recent version (v4.6) was conducted (study No. [T106131-2](#)). It included accessing 62 databases (e.g., ECHA and EPA ECOTOX), which contain about 100,000 chemicals, with more than 3 million measured data points for various endpoints including terrestrial toxicity. It is the largest database and was considered to be the most appropriate for this read-across analysis.

To identify potential read-across candidates, for which appropriate data on terrestrial toxicity is available, two search strategies were followed: a) the complete chemical structure of elinzanetant and b) substructure motifs.

For strategy a), the search parameters were kept broad, e.g., target similarity $\geq 30\%$, while existence of terrestrial data was mandatory, to identify a larger set of potential candidate substances. However, there was no substance with $\geq 50\%$ similarity for which terrestrial data was available and more precisely, there were only 3 potential candidates with 40-50 % structural similarity that had terrestrial toxicity data with them. Also, all of them were by far too dissimilar to be appropriate for read-across to elinzanetant.

For strategy b), three key structural motifs were used in the search and existence of terrestrial data was mandatory. There was one result for the trifluoromethyl benzene motif, but this structure was still too different to be useful. Also, there were no findings for the other two motifs. Read-across search based on structural motifs did not provide additional insights.

In conclusion, two strategies to identify candidates for read-across to elinzanetant were not successful.

6.7.1 Conclusion on the Need of a Terrestrial Assessment

A read-across analysis was conducted to identify potential structurally sufficiently similar substances or structural motifs with terrestrial data, that could be used to determine the need for terrestrial studies/assessment for elinzanetant. Since no appropriate candidates were identified, the read-across analysis could not provide any additional guidance. It was therefore decided that the terrestrial assessment, including conduct of terrestrial studies, needs to be performed, to assess the potential risk from the use of elinzanetant in the terrestrial compartment.

6.8 Environmental Effects

As reported in section [6.6](#) there would be no need to provide an EA based on the EICs calculated for the aquatic and terrestrial compartment. However, a chronic fish study (Zebrafish Extended One Generation Reproduction Test; ZEOGRT) had to be performed to exclude potential effects on the endocrine system of vertebrate species in the environment.

In addition, environmental studies that correspond to tier 3 testing in the FDA Guidance (FDA 1998) were conducted to meet the requirements of other Health Authorities and are included in the EA.

6.8.1 Results of Microbial Inhibition Test

The toxicity of elinzanetant on the activity of an aerobic activated sludge was evaluated by measuring the respiration rate over 3 hours in accordance with OECD 209 test method (report No. [B002708](#)). Test concentrations were (b) (4) ppb elinzanetant. In addition, 1,000, 4,000, and 3,500 ppb of 3,5-Dichlorophenol, and six inoculum controls were assessed. In comparison to the inoculum controls, the total respiration rate of the activated sludge was not inhibited at any test concentrations.

The mean respiration rates of the controls for heterotrophic respiration were in the same range as for total respiration, wherefore in accordance with test method OECD 209, evaluation of the heterotrophic and nitrification respiration is omitted, and total respiration is the only endpoint reported.

All validity criteria were met. The 3-hour EC₅₀ for total respiration was found to be (b) (4) ppb, which is within range recommended by OECD 209 of 2,000-25,000 ppb. The oxygen uptake in the blank controls was 22.2 mg/g/h and therefore clearly above 20 mg oxygen/g of activated sludge (dry weight of suspended solids) in an hour. The respiration rates of the control replicates varied by 13.5 % and remained within 30 % variance as required for the total respiration.

The 3-hour EC_X value for the total respiration could not be established. The LOEC was determined to be higher than the highest test concentration of (b) (4) ppb, the NOEC was reported as (b) (4) ppb ([Table 6–10](#)).

Table 6–10: Microbial inhibition test

Parameter	Duration	Results (ppb)	Method	Report No.
Activated sludge respiration inhibition	30 min	LOEC (b) (4) NOEC (b) (4)	OECD 209	B002708

6.8.2 Results of Aquatic Ecotoxicity Studies

Ecotoxicity of elinzanetant was assessed in chronic aquatic toxicity studies, that were conducted according to OECD test methods and GLP requirements.

Toxicity to algae

Toxicity to algal growth was assessed in an OECD 210 study with the unicellular green algae *Pseudokirchneriella subcapitata* (recently named *Raphidocelis subcapitata*) (report No. [B002234](#)). All validity criteria were met. The study encompassed 6 treatment groups with (b) (4) ppb test item (geometric mean) in triplicates and control and six replicates in a static test system, with exposure over a period of 72 hours. Cell density was spectrophotometrically determined. The NOEC was reported to be ≥ (b) (4) ppb, the LOEC and EC₅₀ as > (b) (4) ppb, all based on growth rate.

Toxicity to crustaceans

In a semi-static reproduction study, toxicity of elinzanetant to the water flea *Daphnia magna* was assessed in accordance with OECD 211 (report No. [B002235](#)). All validity criteria were met. *Daphnia* were exposed to 5 treatment groups at (b) (4) ppb test item (time-weighted average) and a control with 10 replicates, each containing one daphnia. Elinzanetant showed a concentration dependent increase on reproduction of introduced adults, reproduction of surviving adults, and mortality of adults. At the end of the 21-day exposure

period, the results were a NOEC of (b) (4) ppb and a LOEC of (b) (4) ppb, both based on reproduction per introduced daphnia as well as surviving adult.

Toxicity to fish

As aligned with the FDA, the EA considers the draft report of the chronic aquatic toxicity study in fish (ZEOGRT). The final study report will be provided during the 60-day NDA filing review period.

This study report should be considered preliminary in that the study report and raw data have not yet been reviewed by the Quality Assurance Unit (QAU) of the test facility. Moreover, there is ongoing evaluation of limited biomarker related data of vitellogenin (VTG) concentrations in blood plasma of the exposed fish. In addition, statistical analysis of the histopathological data of fish gonads has not yet been completed. However, the limited ongoing work is not expected to change the overall results or conclusions in the draft report.

In detail, a chronic aquatic toxicity study was conducted to assess whether elinzanetant affects the endocrine system in vertebrates. A Zebrafish Extended One Generation Reproduction Test (ZEOGRT) with Elinzanetant (report No. B003372) was performed to assess the effects of continuous exposure to the test item on different life stages and life performances of zebrafish (*Danio rerio*) during a multi-generation approach, including the spawning period of the parental generation (F0), early life stages, juvenile growth, sexual maturation, and reproduction of the first filial generation (F1-generation), and the early embryonal stage of the second filial generation (F2-generation).

The study followed the ZEOGRT OECD test protocol developed under OECD test method project 2.59 (5). The test protocol is currently under validation by the OECD. The study was conducted at the CRO (b) (4)

(b) (4) This CRO ensures that the study was in line with the draft OECD test method and considering latest developments.

The test was performed under flow through conditions. Zebrafish (*Danio rerio*) were exposed to elinzanetant at (b) (4) nominal concentration, corresponding to (b) (4) ppb effective concentration (mean measured) and completed with a control. The treatment lasted for 131 days. There were 4 replicates per treatment and control, with 5 male fishes and 5 female fishes each.

Test conditions were monitored during the course of the study. Water temperature was in the range of 25.7 °C to 26.8 °C in all test vessels, did not differ by more than ± 2.0 °C between successive days at any time during the test, and was within 26.0 ± 2.0 °C. The oxygen saturation in all test vessels was between 86 % and 105 %. The pH in the test vessels was between 7.04 and 8.20. The photoperiod was 12 h light / 12 h dark, with a light intensity of approx. 1000 lux, 5 cm above water surface in the middle of each vessel.

Fish groups were held under test conditions for at least 7 days prior to test, to record spawning success during the pre-treatment phase. Fish were fed *ad libitum* with commercially available flake food and brine shrimp nauplii (*Artemia salina*), provided at interval of at least 4 hours.

A validated LC-MS/MS method was used for chemical analysis of water samples to verify the actual exposure concentration over the course of the study. The limit of quantification (LOQ) on test sample level was (b) (4) ppb and the limit of detection (LOD) on test sample level was set to (b) (4) ppb (b) (4) % of LOQ).

Endpoints that were determined included hatching success and rates, mortalities during different life stages, and juvenile growth (F1-generation, only). The sex ratio was determined

by macroscopic inspection of gonads and by histological analysis (F0/F1-generation) of the fish. Spawning performance (fecundity) and fertilization rate was recorded for adult fish of F0 and F1-generation. The time to first spawning was recorded for the F1-generation. Blood plasma samples of the adult fish of F0- and F1-generation were taken and measured for vitellogenin (VTG) concentration. Furthermore, a histopathological examination of the fish gonads of the adult fish of the F0- and the F1-generation was performed.

All validity criteria were met.

From the results obtained, the threshold concentrations of Elinzanetant per endpoint were determined, i.e., the concentration with significant observed sublethal or lethal toxic effects (LOEC) and the highest concentration tested without any significant effects (NOEC). All statistics were calculated using the most recent version of ToxRat® Professional (v3.3). For NOEC / LOEC determination, quantal data were arcsine-transformed prior to analysis. NOEC were calculated, using ANOVA, followed by Dunnett's test if no concentration-response relationship was observed or the Williams test if a concentration-response relationship was observed, or respective non-parametric approaches (e.g. Jonckheere-Terpsta test). EC₁₀ values could not be established, due to missing effects up to the highest test concentration or effects at higher test concentrations with no sufficient concentration-response relationship.

No effects were observed for most of the endpoints assessed up to the highest test concentration, resulting in $\text{NOEC} \geq \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ (mean measured). The reported effects were based on systemic toxicity and there were no indications for specific effects on the endocrine system. Therefore elinzanetant is not an EAS. Statistically significant effects were reported for F0 fertilisation rate ($\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ mean measured), F0 wet weight in female fish ($\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ mean measured), F0 total length in female fish ($\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ mean measured), F0 vitellogenin levels in male fish ($\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ mean measured), F1 survival at day 21 pdf and day 35 dpf ($\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ mean measured), F1 total length at day 35 ($\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ mean measured) and F1 fertilisation rate ($\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ mean measured).

The effects on the F0- and F1-generation fertilisation rate were minor and not considered population relevant, as the rates of both generations were well within the fertilisation rates determined in control fish in the test method validation studies at the test facility.

To conclude, population relevant systemic toxicity manifested as reduced growth of the F1 generation in this study with a $\text{NOEC} = \text{[REDACTED]}^{(b) (4)} \text{ ppb}$ (mean measured).

There was no evidence of specific endocrine related activity or adversity on fish, exposed to elinzanetant in this extended one generation study.

Conclusion on Aquatic Ecotoxicity Studies

The lowest aquatic chronic toxicity effect level in all aquatic chronic toxicity studies was reported with fish (*Danio rerio*) in the ZEOGRT study and a $\text{NOEC}_{\text{aquatic}} \text{ of } \text{[REDACTED]}^{(b) (4)} \text{ ppb}$, which was used to calculate the PNEC in the aquatic compartment.

Table 6–11: Aquatic Ecotoxicity studies

Study	Duration	Result (ppb)	Method	Report No.
Algae (<i>Pseudokirchneriella subcapitata</i>) growth inhibition	72 h	ErC ₅₀ > (b) (4) LOEC > (b) (4) NOEC ≥ (b) (4) (growth rate)	OECD 201	B002234
Crustacean (<i>Daphnia magna</i>) reproduction	21 d	LOEC = (b) (4) NOEC = (b) (4) (reproduction)	OECD 211	B002235
Fish (zebrafish, <i>Danio rerio</i>) Extended one generation study	131 d	LOEC = (b) (4) NOEC = (b) (4) (growth)	ZEOGRT ¹	B003372

¹ OECD test protocol developed under OECD test method project 2.59 (5).

6.8.3 Additional Ecotoxicological Data

Sediment toxicity

According to the FDA guidance for human pharmaceuticals (1), a sediment assessment is not required. Existing sediment toxicity data is reported in the EA for data transparency reasons.

Toxicity to sediment dwelling organisms was assessed in a study that was conducted in accordance with OECD test method 218 (report No. B003366). For this purpose, first instar larvae of *Chironomus riparius* were exposed in a sediment-water system to 5 test concentrations of (b) (4) ppm, a solvent control, and a control. The replication was 4 for each test concentration and the blank control as well as 6 for the solvent control, each containing 20 larvae. The larvae were exposed for 28 days. The effect on full maturation of the larvae to adult midges, based on number of adult midges emerged (emergence rate) and the time to emergence (development rate), were recorded. The sediment was spiked with the test item to simulate its presence in the sediment. The concentrations of the test item were determined in the overlying water, the pore water and the sediment of all test concentrations and the controls from test start and test end, to inform on the behavior / partitioning of the test item in the water-sediment system.

The quantification of the test item in the test samples was performed using liquid chromatography with MS/MS detection. The test item was mainly found in the sediment. In pore water and overlying water, only small amounts of the test item were measured.

All validity criteria were met. The 28-day NOEC for the rates of emergence and development was determined to be (b) (4) ppm, with an associated LOEC of (b) (4) ppm (Table 6–12).

Table 6–12: Additional Aquatic Ecotoxicity Studies

Study	Duration	Res (b) (4) nm)	Method	Report No.
Non-biting midge (<i>Chironomus riparius</i>) emergence, development	28 d	LOEC = (b) (4) NOEC = (b) (4) (emergence, development)	OECD 218	B003366

Bioaccumulation in fish

In addition to the chronic aquatic toxicity, the bioaccumulation of elinzanetant was determined in an aqueous exposure study according to OECD TG 305 (report No. B003370),

using ^{14}C -labelled test item. Zebrafish (*Danio rerio*) were exposed at 3.5 ppb under flow-through conditions during the uptake phase which took 15 days. A solvent control group was conducted in parallel. The test was performed in 19 L tanks with at least 5-fold water exchange per day. The exposure phase was followed by a depuration phase which lasted 32 days. Chemical analysis was performed using LSC for total radioactivity and HPLC coupled with radio detection for test item specific concentrations. The test item concentration was at least a factor 10 below the LOD of the LSC method.

The time-weighted average (TWA) concentration was 1.8 ppb, i.e., 51 % of the nominal concentration. The TWA varied by up to 17 %, being sufficiently within the required boundaries of ± 20 %.

Steady state concentrations were based on mean tissue concentrations of days 8, 12, and 15 of the bioaccumulation uptake phase. The whole body mean test item concentration during the uptake phase based on total radioactivity was 0.155 mg/kg (steady state).

The mean lipid content of the fish at the end of the study was 8.2 %, wherefore BCF were normalized to a lipid content of 5 % in the study report. The study reported several BCF values:

- a) based on steady state (SS):
 - $\text{BCF}_{\text{SS}} = 86.2$
 - $\text{BCF}_{\text{SSL}} = 52.7$ (lipid normalised),
- b) Based on kinetics (K):
 - $\text{BCF}_{\text{K}} = 103$
 - $\text{BCF}_{\text{Kg}} = 103.1$ (growth corrected)
 - $\text{BCF}_{\text{KL}} = 62.9$ (lipid-normalised)
 - $\text{BCF}_{\text{KgL}} = 62.9$ (lipid-normalised and growth-corrected)
 - $\text{T1/2}_g = 1.3$ days

In general, the growth-corrected and lipid normalized kinetic BCF is preferred over the steady-state BCF, wherefore the BCF of 62.9 can be used to conclude on the bioaccumulation potential.

6.8.4 Results of Terrestrial Ecotoxicity Studies

As the read-across analysis (section 6.7) did not provide relevant lead, a terrestrial assessment was conducted in accordance with the FDA feedback received for the Type D meeting.

Seedling emergence

A seedling emergence study according to OECD 208 was conducted to assess toxicity of elinzanetant to terrestrial plants (report No. B003379). Semen of 7 plant species, representing 6 plant families, including 5 dicotyledons (*Brassica napus*, *Brassica oleracea*, *Glycine max*, *Cucumis sativus*, *Helianthus annuus*,) and 2 monocotyledons (*Avena sativa*, *Allium cepa*), were exposed for 21 days. Depending on the species, 2 to 5 seeds per pot with 4 to 10 replicates were sown, summing up to 20 or 21 tested seeds per treatment group. Seedlings were split in two groups that required similar test conditions (e.g., temperature, humidity, and light) and grown in a growth chamber under controlled conditions.

Depending on the results for each species in the range finding study (conducted at 1,000 ppm) exposure concentrations in the main study were defined, ranging between 0.46 and 1,000 ppm

and completed with a control. *Cucumis sativus*, *Helianthus annuus*, and *Avena sativa* were tested at the limit test concentration of 1,000 ppm. Endpoints were fresh weight, emergence, and mortality of the plants. All validity criteria were met.

There were no effects on seedling emergence and phytotoxicity with all species. The lowest effect level was determined with *Glycine max* based on fresh weight. The NOEC established at (b) (4) ppm, the LOEC at (b) (4) ppm, and the EC₁₀ at (b) (4) ppm.

Earthworm reproduction

As recommended by the Agency in the Type D Meeting, toxicity of elinzanetant to earthworm reproduction was determined in a study conducted in accordance with OECD test method 222 (report No. B003351). *Eisenia andrei* earthworms were exposed in artificial soil to 1.71, 3.09, 5.56, 10.0, 18.0, 32.4, 58.3 and 105 ppm and a control. Replication was 4 per treatment and 8 for the control. The assessed endpoints were adult earthworm mortality, behavioural effects, and biomass development after 28 days exposure of adult earthworms in treated artificial soil. The reproduction rate (number of offspring) was assessed after an additional 28 days, i.e., 56 days after exposure to the test item.

The artificial soil initially had a pH of 5.8 to 6.3, while the pH at experimental end was 6.4 to 6.5. The water content was 24.9 % to 26.5 % (52.9 % to 56.4 % of maximum water holding capacity, WHC) at start of the experiment and 23.3 % to 25.7 % (49.6 % to 54.7 % of the maximum WHC) at the end. The temperature ranged between 18 °C to 22 °C. The photoperiod was 16 h light / 8 h dark, with a light intensity of 400 to 800 lux.

No statistically significant effects were observed on mortality, body weight, or reproduction and there were no observations of behavioural effects at any treatment concentration compared to control. Feeding activity was unremarkable as well.

The NOEC for all endpoints was thus reported as (b) (4) mg/kg soil and the LOEC as (b) (4) mg/kg soil, both based on dry weight. The EC₁₀ could not be established.

Toxicity to microorganisms

Inhibition of nitrogen transformation with soil micro-organisms was assessed in a study conducted in accordance with OECD test method 216 (report No. B003102). Biologically active agricultural soil (loamy sand) was exposed for 28 days to control and treatments of (b) (4) mg/kg dry weight, each in triplicates. All validity criteria were met.

The test item had no inhibiting impact on nitrogen transformation (nitrate-N content, nitrate-N formation rate) of soil microorganisms when applied at test item concentrations up to and including 1000 mg/kg soil dry weight treatment.

Therefore, the NOEC for inhibiting effects on nitrate transformation (nitrate content and nitrate formation rate) appears to be (b) (4) ppm on dry weight basis. EC_X could not be established.

Conclusion

The lowest chronic toxicity effect level among all terrestrial studies was reported with plants (*Glycine max*) and the EC₁₀ of (b) (4) ppm was used to calculate the PNEC for the terrestrial compartment.

Table 6–13: Terrestrial toxicity studies

Study	Duration	Result (ppm dry weight)	Method	Report No.
Terrestrial plants (<i>Brassica napus</i> , <i>Brassica oleracea</i> , <i>Glycine max</i> , <i>Cucumis sativus</i> , <i>Helianthus annuus</i> , <i>Avena sativa</i> , <i>Allium cepa</i>) growth	21 d	LOEC NOEC EC ₁₀ = (b) (4)	OECD 208	B003379
Earthworm (<i>Eisenia andrei</i>) reproduction	56 d	LOEC NOEC (b) (4)	OECD 222	B003351
Soil micro-organisms: (<i>natural soil</i>) Nitrogen transformation	28 d	LOEC NOEC (b) (4)	OECD 216	B003102

6.9 Risk Assessment

(b) (4)

6.10 Summary of Environmental Effects Tests

Aquatic compartment

The study on aquatic chronic toxicity in fish (ZEOGRT) reported systemic toxicity at the highest concentrations but no endocrine effects and therefore elinzanetant is not an endocrine disrupting substance.

Elinzanetant caused no inhibitory effect with algae and micro-organisms up to the highest test concentrations of (b) (4) ppb and (b) (4) ppb, respectively. There was a toxic effect on reproduction of crustaceans with a NOEC of (b) (4) ppb. The lowest effect level among chronic aquatic toxicity data however was determined with fish and a NOEC of (b) (4) ppb.

There were two additional studies reporting assessment, which are not part of an EA: A study on toxicity in sediments reported moderate toxicity to sediment organisms, while a study on bioaccumulation potential in fish established a low potential for bioaccumulation for elinzanetant.

The risk quotients (RQ) in the aquatic environment were calculated with the EIC and the EEC, considering the PNEC derived with the lowest NOEC in the chronic fish study. Both RQ were (well) below 1 and revealed no risk in the aquatic environment. The EA is expected to be complete, and no further work is required.

Terrestrial compartment

There were no indications for effects on the endocrine system of the relevant test organisms (earthworms) in terrestrial studies.

In earthworms and soil micro-organisms, elinzanetant caused no effects up to the highest test concentrations of (b) (4) ppm, respectively. Toxicity was observed in some plants at high concentrations resulting in an EC₁₀ of (b) (4) ppm, that was used to calculate the PNEC.

The risk quotient (RQ) in the terrestrial environment was calculated with the EIC_{terrestrial} and the PNEC_{terrestrial} derived with the lowest NOEC in the terrestrial study. The RQ_{terrestrial} was well below 1 and revealed no risk in the terrestrial environment. The EA is therefore expected to be complete, and no further work is required.

7. Mitigation Measures

The EA revealed no risk from the use of elinzanetant in the aquatic or terrestrial environment. Hence, specific mitigation measures are not required.

Environmental impacts associated with the disposal of the API and/or metabolites following consumption in humans will be mitigated by conventional wastewater treatment plants or in



some cases septic systems. Rejected, unused or expired product will often be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, in accordance with all federal, state, and local regulatory requirements, although minimal quantities of unused drug could be disposed of in the sewer system.

8. Alternatives to the Proposed Action

No potential environmental impacts were identified from the use of elinzanetant.

There appear to be two alternatives by which to respond to this proposed action: Approval of the proposed action through the issuance of a Finding of No Significant Impact (FONSI) or non-approval and notification of intent to prepare an Environmental Impact Statement (EIS). We believe that the first action, issuance of a FONSI, is fully justified considering the data and conclusions provided in this EA.

Manufacturing operations will be in compliance with the regulations of the applicable governmental agencies. Mitigation measures are not required (see section 7). Depletion and ecotoxicity data detailed in section 6 support the position that the manufacture and use of elinzanetant are highly unlikely to cause adverse effects in the environment.

Approval of elinzanetant will enable the new treatment options to be available to patients in need.



9. List of Preparers

(b) (4)

10. References

10.1 Literature

- (1) Guidance for Industry – Environmental Assessment of Human drug and Biologics Applications. US Dept Health and Human Services; Food and Drug Administration; CDER; CBER. 1998.
- (2) Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). March 2016. Pharmaceutical Quality/CMC.
- (3) Guidance for Industry. Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) – Phase I. VICH GL6. Final Guidance. <https://www.fda.gov/media/70340/download>
- (4) Guidance for Industry: Appendix A of Preparing a Claim of Categorical Exclusion or an Environmental Assessment for Submission to CFSAN. May 2006. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-appendix-preparing-claim-categorical-exclusion-or-environmental-assessment>
- (5) Work plan for the OECD Test Guidelines Programme (TGP). September 2023. <https://www.oecd.org/chemicalsafety/testing/work-plan-test-guidelines.pdf>
- (6) Biran J, Palevitch O, Ben-Dor S, et al. (2012) Neurokinin Bs and neurokinin B receptors in zebrafish-potential role in controlling fish reproduction. *Proc. Natl. Acad. Sci. USA.* 109 (26):10269-10274. <https://doi.org/10.1073/pnas.1119165109>
- (7) Goodman RL, Hileman SM, Nestor CC, et al. (2013) Kisspeptin, Neurokinin B, and Dynorphin Act in the Arcuate Nucleus to Control Activity of the GnRH Pulse Generator in Ewes. *Endocrinology.* 154 (11):4259-4269 <https://doi.org/10.1210/en.2013-1331>
- (8) Hu G, Lin C, He M, et al. (2014) Neurokinin B and reproductive functions: “KNDyneuron” model in mammals and the emerging story in fish. *General and Comparative Endocrinology.* 208:94-108. <https://doi.org/10.1016/j.ygcen.2014.08.009>
- (9) Li Y, Zhao T, Liu Y, et al. (2021) Knockout of *tac3* genes in zebrafish shows no impairment of reproduction. *General and Comparative Endocrinology.* 311:113839. <https://doi.org/10.1016/j.ygcen.2021.113839>
- (10) Ogawa S, Ramadasan PN, Anthonysamy R and Parhar IS (2021) Sexual Dimorphic Distribution of Hypothalamic Tachykinin1 Cells and Their Innervations to GnRH Neurons in the Zebrafish. *Front. Endocrinol.* 11:534343. <https://doi.org/10.3389/fendo.2020.534343>

- (11) Young J, George JT, Tello JA, et al. (2013) Kisspeptin restores pulsatile LH secretion in patients with neurokinin B signaling deficiencies: physiological, pathophysiological and therapeutic implications. *Neuroendocrinology*. 97:193-202. [https:// doi.org/10.1159/000336376](https://doi.org/10.1159/000336376)
- (12) Zhou W, Li S, Liu Y, et al. (2012) The evolution of tachykinin/tachykinin receptor (TAC/TACR) in vertebrates and molecular identification of the TAC3/TACR3 system in zebrafish (*Danio rerio*). *Mol. Cell. Endocrinol.* 361 (1-2):202-212. [https:// doi.org/10.1016/j.mce.2012.04.007](https://doi.org/10.1016/j.mce.2012.04.007)

10.2 Reports

Report No.	Title	Company	Department	Study no.
R-14369	BAY 3427080: Determination of the Water Solubility by Column Elution Method at pH 4, 5, 7 and 9	Bayer AG	Experimental Toxicology	T105486-4
R-14295	BAY 3427080: Determination of the Vapour Pressure by Isothermal Thermogravimetry	Bayer AG	Toxicology	T105485-3
B002064	BAY 3427080: Determination of the Partition Co-efficient (<i>n</i> -Octanol/Water) by the Slow Stirring Method buffered at pH 4, 5, 7 and 9	Bayer AG	Ecotoxicology	T105487-5
R-14250	BAY 3427080: Adsorption/Desorption Behaviour in Soil using a Batch Equilibrium Method [OECD 106]	Bayer AG	Experimental Toxicology	T105492-1
B002189	Determination of physico-chemical properties. Dissociation constants in water	Bayer AG	Toxicology	T105488-6
R-14426	BAY 3427080: Hydrolysis as a Function of pH [OECD 111]	Bayer AG	Ecotoxicology	T105491-0
R-14371	BAY 3427080: Ready Biodegradability in a Manometric Respirometry Test	Bayer AG	Experimental Toxicology	T105489-7
B002870	[¹⁴ C] BAY 3427080: Aerobic Transformation in Aquatic Sediment Systems [OECD 308]	Bayer AG	Experimental Toxicology	T105493-2
B002234	BAY 3427080: Toxicity to <i>Pseudokirchneriella subcapitata</i> in an Algal Growth Inhibition Test	Bayer AG	Toxicology	T105494-3
B002235	BAY 3427080: Effects on <i>Daphnia magna</i> in a Semi-Static Reproduction Test	Bayer AG	Ecotoxicology	T105495-4

B003372	Zebrafish (<i>Danio rerio</i>), Extended one generation reproduction test (ZEOGRT) with Elinzanetant, Flow through conditions (DRAFT report)	Bayer AG	Experimental Toxicology	T105668-6
B002708	BAY 3427080: Toxicity to Activated Sludge in a Respiration Inhibition Test	Bayer AG	Toxicology	T105497-6
B003370	[¹⁴ C] BAY 3427080: Bioaccumulation in Zebrafish (<i>Danio rerio</i>) – Aqueous Exposure [OECD 305]	Bayer AG	Experimental Toxicology	T105787-8
B003366	BAY 3427080: Effects on the Development of <i>Chironomus riparius</i> in a Sediment-Water System - exposed via spiked Sediment	Bayer AG	Experimental Toxicology	T105994-8
B003351	BAY 3427080: Effects on Reproduction and Growth of Earthworms <i>Eisenia andrei</i> in Artificial Soil	Bayer AG	Experimental Toxicology	T105970-2
B003379	Terrestrial Plant Test: Seedling Emergence and Seedling Growth OECD 208	Bayer AG	Experimental Toxicology	T105971-3
B003102	Soil Microorganisms: Nitrogen Transformation OECD 216	Bayer AG	Ecotoxicology	T105969-0
NA	Read-across analysis for terrestrial studies with the active pharmaceutical ingredient (API) elinzanetant	Bayer AG	Ecotoxicology	T106131-2
PH-42275	Elinzanetant: Biotransformation in Man	Bayer AG	Drug Metabolism and pharmacokinetics	NA

NA – Not applicable



11. Appendix A - Nonconfidential Data

The EA is nonconfidential, except for the data which is indicated in the [Appendix B - Confidential Data](#).

12. Appendix B - Confidential Data

The following data in this EA is considered confidential, including any personal data, data on prognosed sale volumes or numbers that allow sales figures to be calculated. Specifically, this includes:

- **Title page:** Personal data on signatories
- **Section 6.6 – Environmental Concentrations:** The whole section with all numbers and specifically the sale volume forecast data (e.g., [Table 6–8](#)), EIC and EEC.
- **Section 6.8.2 – Results of Aquatic Ecotoxicity Studies (Toxicity to fish section):** Numbers in the summary of the chronic aquatic fish study (ZEOGRT) such as test concentrations or effect levels including EC₁₀, LOEC, and NOEC.
- **Section 6.8.2 – Results of Aquatic Ecotoxicity Studies (Toxicity to fish):** The CRO that conducted the chronic fish study: (b) (4)
- **Section 6.9 – Risk assessment:** The whole section and in particular specific numbers such as EC₁₀, NOEC, PNEC, EIC and EEC.
- **Section 9 – List of Preparers:** The whole section as this is personal data.

13. Appendix C – SimpleTreat Calculation

Input values for elinzanetant used for calculation in SimpleTreat (v4.1.0) and results are provided in the software export datasheet.

SimpleTreat 4 Export file			
Calculation mode:		SimpleTreat 4	
Version:		4.1.0	
Date:		Friday, June 21, 2024	
Input			
Substance	User value	Default value	Unit
Chemical class	Neutral		-
Molecular weight	668,6		g/mole
Octanol-water partition coefficient (Kow)	204174		-
Aparent Kow at actual pH (Dow)			-
Vapour pressure	8E-07		Pa
Vapour pressure used (temp. corrected)	5,604025E-07		Pa
Temperature for determining vapour pressure	293,15	293,15	Kelvin
Solubility (S)	1,7		mg/l
Solubility used (temp. corrected)	1,583182E+00		mg/l
Temperature for determining solubility	293,15	293,15	Kelvin
pKa			-
Henry coefficient (H)		2,366858E-04	Pam3/mole
Henry coefficient used (temp. corrected - only for user value)			Pam3/mole
Temperature for determining Henry coefficient (only for user value)	293,15	2,931500E+02	Kelvin
Organic carbon partition coefficient (Koc)	5388	2,518259E+04	l/kg
Partition coefficient in raw sewage (Kps)		1,816400E+03	l/kg
Partition coefficient in activated sludge (Kpas)		1,993560E+03	l/kg
Mode of operation			
Facility type	Municipal	Municipal	-
Operation mode	Primary solids removal	Primary solids removal	-
Sewage flow (Q)	0,2	0,2	m3/d PE
Mass of sewage solids (SO)	0,09	0,09	kg/d PE
Mass of O2 binding material in sewage (BOD)	60	60	g O2/d PE
Fraction of BOD in sewage solids (FB)	0,5417	0,5417	-
Fraction of sewage solids removed by primary sedimentation (FS)	0,67	0,67	-
Sludge loading rate (kslr)	0,1	0,1	-
pH	7	7	-
Surface or bubble aeration	surface	surface	-
Model parameters			
Surplus sludge	0,02567469086		kg _{sur} PE ⁻¹ d ⁻¹
Biodegradation			
Biodegradation method selected	OECD 301 series, 310, 302 series		-
Biodegradation constant	0		hr-1
Biodegradation constant used (temp. corrected)			hr-1
Temperature for determining biodegradation constant			Kelvin
Biodegradation applies to	Aqueous phase		-
Emission scenario			
Temperature environment	288,15	288,15	Kelvin
Wind speed	3	3	m/s
Number of inhabitants	10000	10000	Person
Emission rate chemical	1	1	kg/d
Output			
Elimination percentages		Value	Unit
Elimination in the primary settler			
Volatilization			0,00 %
Via primary sludge			28,21 %
Total			0,00 %
Elimination in the aerator			
Stripping			0,00 %
Biodegradation			0,00 %
Total			0,00 %
Elimination in the solids liquid separator			
Volatilization			0,00 %
Via surplus sludge			14,45 %
Total			0,00 %
Total elimination from waste water			42,67 %
Total emission via effluent			57,33 %
Balance			0,00 %
Concentrations			
Air			5,83E-11 g/m3
Combined sludge			4,96E+02 mg/kg
Primary sludge			4,88E+02 mg/kg
Surplus sludge			5,83E+02 mg/kg
Raw sewage			5,00E-01 mg/l
Dissolved			2,89E-01 mg/l
Associated			2,11E-01 mg/l
Settled sewage			3,59E-01 mg/l
Dissolved			2,89E-01 mg/l
Associated			6,85E-02 mg/l
Mixed liquor			2,53E+00 mg/l
Dissolved			2,82E-01 mg/l
Associated			2,25E+00 mg/l
Effluent			2,87E-01 mg/l
Dissolved			2,82E-01 mg/l
Associated			4,22E-03 mg/l
In solids effluent			5,83E+02 mg/kg



James
Laurenson

Digitally signed by James Laurenson

Date: 3/21/2025 02:51:40PM

GUID: 51dc6bdb0000c62de59b85452e59746f



Xiaoqin
Wu

Digitally signed by Xiaoqin Wu

Date: 3/21/2025 01:20:09PM

GUID: 625df66f00cc22833bedee13222a2cba



CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	219469
Assessment Cycle Number	1
Drug Product Name	Lynkuet (elinzanetant) capsules, 60 mg

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	SDN 0013
Patient Information	Adequate	SDN 0013
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	SDN 0008
Carton Labeling	Adequate	SDN 0008

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0008	October 29, 2024	C/C labels
0013	November 22, 2024	Labeling, PI, Patient Package

1.0 PRESCRIBING INFORMATION

(b) (4)

Assessment of Product Quality Related Aspects of the Prescribing Information:

Submitted on November 22, 2024 SDN 0013

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)¹	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

1.1 FULL PRESCRIBING INFORMATION

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Inadequate	Replace "LYNKUET capsule" with "LYNKUET (elinzanetant) capsule"
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple- dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state “DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^X ” with x numerical citation to “OSHA Hazardous Drugs.”	N/A	
--	-----	--

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “ <i>Not made with natural rubber latex. Avoid statements such as “latex-free.”</i> ”	N/A	
Include information about child-resistant packaging (if manufacturer choose to include)	N/A	

1.2.6 Manufacturing Information After Section 17 (for drug products)

Distributed by:
Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981 USA

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

Assessment of PI: **ADEQUATE**

As shown in **red** above the edits were made in the PI and conveyed to the NDA applicant.

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ² , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Adequate	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
“Rx only” displayed on the principal display	Adequate	
NDC	Inadequate	Print the NDC Number on the sample blister foil submitted in Sec. 1.14.1 Draft Carton and Container Labels [0008] Sample Blister Foil
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap Overseal, unless a cautionary statement is required.	N/A	



QUALITY ASSESSMENT



If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others if space is available.	N/A	

Assessment of Carton and Container Labeling: **ADEQUATE**

The following comments regarding the container labels should be conveyed to the NDA applicant:

Sample Blister Foil:

- Print the NDC Number on the sample blister foil submitted in Sec. 1.14.1 Draft Carton and Container Labels [0008] Sample Blister Foil



QUALITY ASSESSMENT



Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name¹	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Adequate	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Assessment of Patient Information: *ADEQUATE*

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

OUTSTANDING ISSUES AND RECOMMENDATIONS

The PI, Patient Information and the container labels are **satisfactory** from the CMC perspective.

This NDA is recommended for “Approval” from the CMC labeling perspective.

The following comments regarding the Package Insert should be conveyed to the NDA applicant:

Package Insert:

- Sec. 11 DESCRIPTION
Replace “LYNKUET capsule” with “LYNKUET (elinzanetant) capsule”

The following comments regarding the container/carton labels should be conveyed to the NDA applicant:

Sample Blister Foil:

- Print the NDC Number on the sample blister foil submitted in Sec. 1.14.1 Draft Carton and Container Labels [0008] Sample Blister Foil

Primary Labeling Assessor Name and

Hitesh Shroff

CDER/OPQ/OPQAII/DPQAVII

01-16-2025

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Julia Pinto, Ph.D.

Supervisory Chemist

CDER/OPQ/OPQAII/DPQAVIII



Hitesh
Shroff

Digitally signed by Hitesh Shroff

Date: 1/21/2025 01:48:27PM

GUID: 502d1ab500002afd219fd67e3b9c99c8



Julia
Pinto

Digitally signed by Julia Pinto

Date: 1/21/2025 03:52:16PM

GUID: 5050dbcb00001294a888a4bdc20a3a58



Title:	NDA IQA Template CHAPTER VI-BIOPHARMACEUTICS		
Document ID:	OPQ-ALL-TEM-0047		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	14		



Template Revision: 03

CHAPTER VI: BIOPHARMACEUTICS

Product Information	Elinzanetant soft gelatin capsule
NDA Number	219469
Assessment Cycle Number	1
Drug Product Name/ Strength	Elinzanetant soft gelatin capsule/60 mg
Route of Administration	Oral
Applicant Name	Bayer HealthCare Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	DUOG
Proposed Indication	Treatment of moderate to severe vasomotor symptoms associated with menopause

Assessment Recommendation: Adequate

Assessment Summary:

The Applicant intends to seek approval of immediate-release Elinzanetant (BAY 3427080) soft gelatin capsule 60 mg for the treatment of moderate to severe vasomotor symptoms associated with menopause *via* the 505 (b)(1) pathway. During transfer of the compound from prior companies to Bayer AG, the compound name has been changed. Therefore GSK1144814, NT-814, BAY 3427080 and elinzanetant are used synonymously to describe the same drug product. Elinzanetant is a selective antagonist at both human NK-1 and NK-3 Neurokinin (NK) receptors. Neurokinin receptors are G-protein coupled receptors that have been pharmacologically classified into NK-1, NK-2 and NK-3 receptor subtypes; their structurally related peptide ligands are, respectively, Substance P (SP), neurokinin A (NKA) and neurokinin B (NKB). Within this NDA, Bayer is providing clinical data from all completed studies including study reports for 24 Phase 1, 2 Phase 2 (RELENT 1 and SWITCH 1) and 3 Phase 3 (OASIS 1, 2 and 3) studies. (b) (4)

(b) (4)

Biopharmaceutics review is focused on the evaluation and acceptability of bridging of formulations, dissolution method, and acceptance criterion.

In Vitro Dissolution Method and Acceptance Criterion: ADEQUATE

The following dissolution method and acceptance criterion are acceptable for the proposed drug product for Quality Control (QC) purposes. The Applicant has provided justification for the selected dissolution method parameters.

Apparatus	Speed (RPMs)	Volume/Medium/Temperature	Acceptance criterion
II (Paddle) with sinker (Stainless Steel, spiral)	75	<u>Tier-I</u> 900 mL 0.8% SDS in 0.1 N HCl/ 37°C ± 0.5°C <u>Tier-II</u> Step 1: 450 mL 0.1 N HCl with pepsin enzyme Step 2: 450 mL 0.1 N HCl with 1.6% SDS	Q=(b) % in 30 minutes

Formulation development and bridging: ADEQUATE from Biopharm perspective

Elinzanetant was initially formulated as suspension, tablets, or hard gel capsules to support earlier clinical studies including Phase 1 studies and the Phase 2a study RELENT-1. Later, a soft gel capsule formulation of different strengths (25, 40 mg and 60 mg) was used in subsequent Phase 1 studies and the Phase 2b study SWITCH-1. Soft gel capsule (b) (4)

The 60 mg soft gel capsule was finally selected for Phase 3 (b) (4) for administration of the 120 mg therapeutic dose. Similar relative oral bioavailability of elinzanetant 120 mg dose was confirmed for the 40 mg (3 x 40 mg) and 60 mg (2 x 60 mg) dose strength soft gel capsule formulations in two independent studies after single and multiple dose administrations. This allowed the bridging of pharmacokinetic (PK) and pharmacodynamic (PD) results from the 40 mg capsule in early Phase 1 and Phase 2b (SWITCH-1) studies to the results from the to-be-marketed 60 mg capsule in Phase 3 studies. The dissolution profiles of elinzanetant capsules 40 mg and 60 mg used in the two relative bioavailability studies 21665 and 22050 and several Phase 1 and pivotal Phase 3 clinical studies showed similar in vitro dissolution profiles.

Finally, Pivotal Phase 3 formulation and commercial formulations are same. The dissolution profiles for elinzanetant 60 mg soft gel capsules manufactured at the clinical site and at the commercial site including scale-up are similar.

Biowaiver Request: Not Applicable

Biowaiver request is not applicable as the Applicant submitted only one strength for approval.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 (Original submission)	07/26/2024

Highlight Key Issues from Last Cycle and Their Resolution: None. This is the first review cycle.

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment: Adequate

The Applicant has not claimed or requested any BCS classification for their drug product. However, following information is provided in M.2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods). Based on the solubility of elinzanetant in aqueous media and its permeability in Caco-2-cells, the compound can be classified as BCS class 2 according to the definition of the Biopharmaceutics Classification System (ICH 2020).

Solubility:

Elinzanetant is (b) (4) showing strong pH-dependent solubility. Elinzanetant is slightly soluble as a protonated cation under acidic conditions whereas the free base is insoluble at neutral pH. Solubility of elinzanetant in aqueous media is shown below.

Table 1: Solubility of elinzanetant in aqueous media

Solvent	Solubility [mg/L] ¹⁾	Solubility descriptor ²⁾
Water ¹⁾	< 0.15	practically insoluble
0.1M HCL	7530	slightly soluble
Buffer pH 2	319	very slightly soluble
Buffer pH 3	85	practically insoluble
Buffer pH 4.5	20	practically insoluble
Buffer pH 7	< 0.15	practically insoluble
Buffer pH 8	< 0.15	practically insoluble

¹⁾ after 24 h, 25°C

²⁾ Ph. Eur. statement of solubility

Similar pH-dependent solubility is also observed with biorelevant media, as shown below. Therefore, elinzanetant can be considered as a low solubility compound.

Table 2: Solubility of elinzanetant in biorelevant media

Medium	Solubility [mg/L] ¹⁾	Solubility descriptor ²⁾
FaSSIF (pH 6.5)	21	practically insoluble
FeSSIF (pH 5.0)	223	very slightly soluble
FaSSGF (pH 1.6)	1247	slightly soluble

¹⁾ after 24 h, 37°C

²⁾ Ph. Eur. statement of solubility

FaSSIF: fasted state simulated intestine fluid, FaSSGF: fasted state simulated gastric fluid, FeSSIF: fed state simulated intestine fluid

Permeability:

Cell permeability of elinzanetant and several reference compounds was determined in Caco-2 cell monolayers. Reference compounds with high (fluvastatin, propranolol) and low permeability

(sulfasalazine, atenolol and cimetidine) were tested in parallel to enable the direct comparison with the in vitro permeability of elinzanetant. The apparent permeability of elinzanetant in apical to basolateral direction (PappAB) ranged between 123 nm/s and 164 nm/s in the concentration range between 0.2 and 10 µM. Hence, elinzanetant was classified as highly permeable. The permeability in the opposite direction (PappBA) was determined to range between 85.6 nm/s and 99.1 nm/s, which resulted in calculated efflux ratios between 0.521 and 0.743. Thus, data from the Caco-2 assay system does not indicate active efflux transport across the cell monolayer.

Dissolution: See below

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

The Biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criterion for elinzanetant soft gel capsules.

Proposed dissolution method and acceptance criterion

The following dissolution method and acceptance criterion were proposed:

Apparatus	Speed (RPMs)	Volume/Medium/Temperature	Acceptance criterion
II (Paddle) with sinker (Stainless Steel, spiral)	75	<u>Tier-I</u> 900 mL 0.8% SDS in 0.1 N HCl/ 37°C ± 0.5°C <u>Tier-II</u> Step 1: 450 mL 0.1 N HCl with pepsin enzyme (activity 750,000 Units/L) Step 2: 450 mL 0.1 N HCl with 1.6% SDS	Q ^{(b) (4)} % in 30 minutes

Elinzanetant soft gel capsules are immediate release solid dosage forms. Elinzanetant drug

(b) (4)

(b) (4). The in vitro dissolution occurs fast and can be classified as rapid to very rapid.

(b) (4)

(b) (4)

Dissolution method development

The Applicant provided justification for each selected dissolution parameter. A summary of the dissolution method development is provided below.

(b) (4)

Discriminating ability of the dissolution method

Influence of the particle size distribution of the API

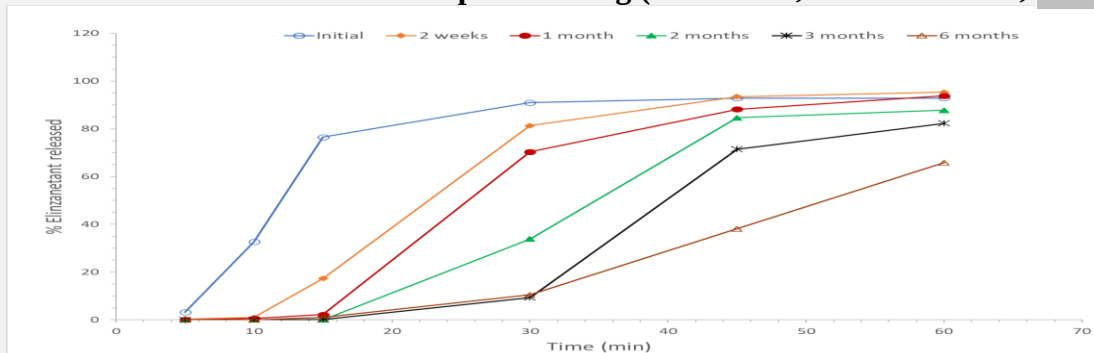
Elinzanetant capsule 60 mg contain a (b) (4)
(b) (4) Therefore, the particle size distribution of the active ingredient will not have any impact on the drug product performance and was therefore not investigated for discriminating ability of the dissolution method.

Influence of crosslinking of the gelatin shell

Elinzanetant capsule 60 mg (#18MC-25) were aged for approximately 72 hours in 75% relative humidity at ambient temperature and were also exposed to formaldehyde vapor in a closed desiccator chamber prepared with 36.5-38.0% formaldehyde solution placed in a glass petri dish at the base of the desiccator at ambient temperature. The dissolution method is indicative of crosslinking as can be seen by the resulting dissolution profiles below.

Figure 8: Dissolution of Elinzanetant capsules 60 mg (#20MC-55; 40 °C/75% RH;

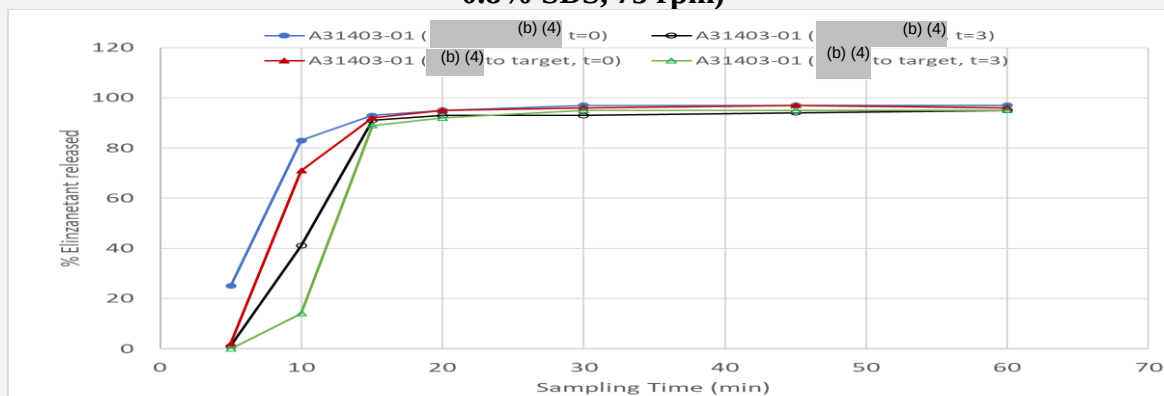
(b) (4)



Influence of (b) (4) of the soft gelatin capsules after manufacturing

A commercial scale technical batch of Elinzanetant capsule 60 mg was manufactured and parts of the capsules were (b) (4). These capsules were placed on an accelerated stability study. The resulting dissolution profiles at start of the study (t=0) and the profiles after 3 months storage at 40 °C/75% RH are shown in the figure below.

Figure 9: Dissolution profiles of 60 mg capsules after different (b) (4) (0.1 M HCl, 0.8% SDS, 75 rpm)

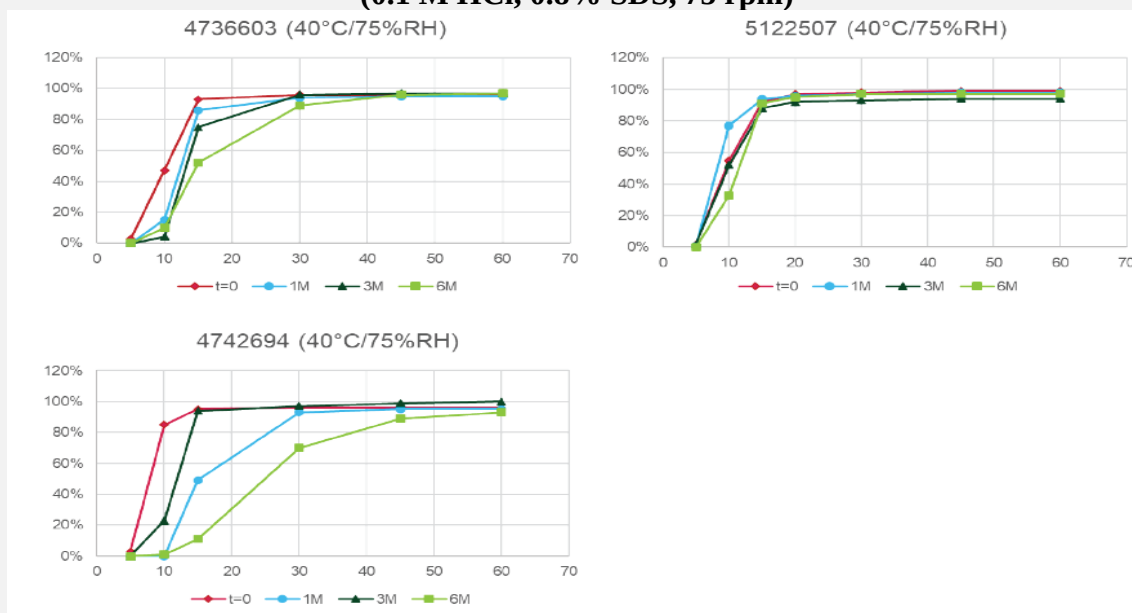


Both test groups differed significantly in the early release profile which resembles the (b) (4) (b) (4) and may indicate slight differences in (b) (4) as a result of different (b) (4). However, all samples met the proposed acceptance criterion of $Q = \frac{(b) (4)}{(4)}\%$ after 30 min.

Influence of accelerated stability testing

Elinzanetant capsule 60 mg have been placed in stability studies and in accelerated storage conditions (40 °C/75% RH). For the final drug product e.g., from primary stability batches stored under accelerated conditions, various extent of crosslinking were seen (Figure 10), all profiles presented are from Tier I testing. The profiles at accelerated storage are indicative of normal manufacturing variability and are also characteristic of long term storage results. Therefore, the discriminating ability of the dissolution test method with respect to ageing effects of the gelatin shell is confirmed.

Figure 10: Mean dissolution profiles; influence of storage at accelerated conditions (0.1 M HCl, 0.8% SDS, 75 rpm)

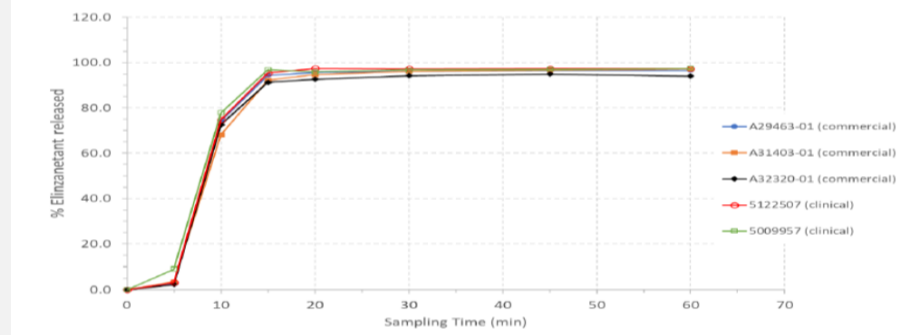


All dissolution test methods used for release of clinical samples and proposed for commercial use were validated according to ICH Guideline Q2(R2).

Dissolution acceptance criterion

The elinzanetant dissolution acceptance criterion is $Q = \frac{(b) (4)}{(4)}\%$ in 30 min for release and shelf-life. Based on the dissolution profile data provided for registration and clinical batches (figure below), the proposed dissolution acceptance criterion is acceptable.

Figure 11: Mean dissolution profiles of clinical and commercial batches



In conclusion, the Applicant has developed a dissolution method for the release of elinzanetant from Elinzanetant soft gelatin capsule. The method is sensitive to changes in gelatin cross linking and accelerated stability that could potentially influence the release of elinzanetant from the capsule. The proposed method is suitable as a QC method for release and stability testing.

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

Early development formulations

Below table provides an overview of formulations used in clinical studies (Phase 1 to 3).

Table 1-2: Formulation information

Formulation (sponsor company)	Study No.
Oral suspension / (b) (4) (GSK)	21673 Single ascending dose study 21674 Multiple ascending dose study
(b) (4) 100 and 200 mg IR tablet (GSK)	21675 PK/food interaction study 21676 Alcohol interaction study
25 mg soft gel capsule (NeRRe) 50 mg hard gel capsule (NeRRe)	21677 Relative bioavailability and food effect study
40 mg soft gel capsule (NeRRe)	21678 Multiple ascending dose study incl. food effect 21679 DDI with itraconazole 21680 Study to investigate the effect on sex hormones 21703 Metabolite PK study 21686 SWITCH-1: efficacy, safety, and PK in females with VMS
50 mg hard gel capsule (NeRRe)	21681 RELENT-1: PK/PD in women with VMS
40 and 60 mg soft gel capsule (Bayer AG)	21665 Relative bioavailability study 22050 Relative bioavailability study 21774 PK in Japanese women
60 mg soft gel capsule (Bayer AG)	21666 DDI with rosuvastatin 21667 DDI with carbamazepine 21668 PK in participants with impaired hepatic function 21669 PK in participants with impaired renal function 21670 Supratherapeutic dose study 21756 PK in Chinese women 21772 DDI with esomeprazole and absolute bioavailability 21840 DDI with midazolam 22004 DDI with tamoxifen and its metabolites 22081 DDI with dabigatran etexilate 21651 OASIS-1: Phase 3 efficacy and safety study [26 weeks] 21652 OASIS-2: Phase 3 efficacy and safety study [26 weeks] 21810 OASIS-3: Phase 3 efficacy and safety study [52 weeks] 22653 Driving study
Special Formulations	
[¹⁴ C]elinzanetant oral suspension (NeRRe)	21664 Mass balance and PK study
[¹³ C ₅]elinzanetant i.v. solution (Bayer AG)	21772 DDI with esomeprazole and absolute bioavailability

All clinical studies mentioned in this table are listed in [Module 5.2](#) and clinical study reports are included in [Module 5.3](#).

Elinzanetant was initially formulated as suspension, tablets or hard gel capsules to support earlier clinical studies including Phase 1 studies and the Phase 2a study RELENT-1.

Elinzanetant soft gel capsule formulations from Phase 1 to 3

Later, a soft gel capsule formulation of different strengths (25, 40 mg and 60 mg) was used in subsequent Phase 1 studies and the Phase 2b study SWITCH-1 as follows:

- a 25 mg soft gel capsule (purpose: Phase 1)
- a 40 mg soft gel capsule (purpose: Phase 1 / 2b [SWITCH-1]) and
- a 60 mg soft gel capsule (purpose: Phase 1, Phase 3 and to-be-marketed formulation)

Soft gel capsule with elinzanetant drug substance (b) (4) was developed due to (b) (4) observed with the elinzanetant (b) (4) capsule formulations.

The 60 mg soft gel capsule was finally selected for Phase 3 to (b) (4) for administration of the 120 mg therapeutic dose. Similar relative oral bioavailability of elinzanetant 120 mg dose was confirmed for the 40 mg (3 x 40 mg) and 60 mg (2 x 60 mg) dose strength soft gel capsule formulations in two independent studies after single and multiple dose administrations. This allowed the bridging of PK and pharmacodynamic PD results from the 40 mg capsule in early Phase 1 and Phase 2b (SWITCH-1) studies to the results from the to-be-marketed 60 mg capsule in Phase 3 studies.

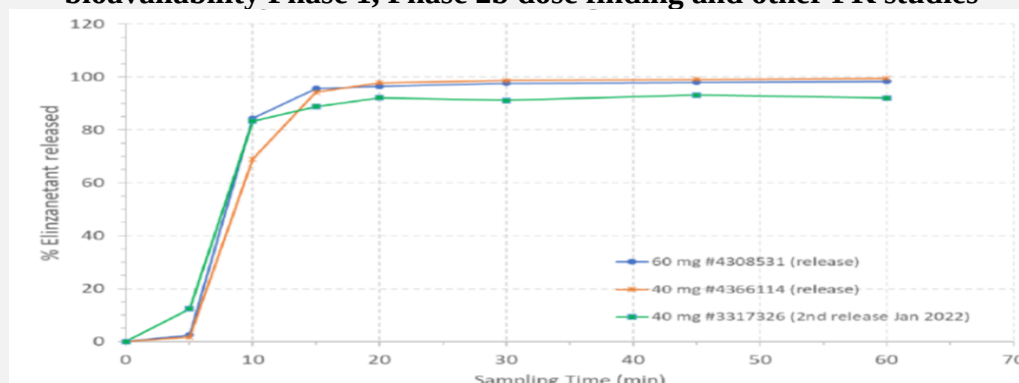
The composition of the 25, 40 mg and 60 mg strengths is shown below:

Table 1-3: Composition of elinzanetant soft gel capsule 25 mg, 40 mg and 60 mg [values in mg]				
Composition	Function	Quantity per capsule [mg]		
		25 mg	40 mg	60 mg
Elinzanetant	Drug substance	25.00	40.00	60.00
Excipients fill mass				(b) (4)
all-rac- α -Tocopherol				
Caprylocaproyl				
macroglycerides				
Glycerol				
monocaprylocaprate				
Glycerol mono-oleate				
Polysorbate 80				
Weight capsule fill			(b) (4)	1200.00
Weight capsule shell	Soft gel capsule			640.13
Weight capsule				1840.13

The dissolution profiles of elinzanetant capsules 40 mg and 60 mg used in the two relative bioavailability studies 21665 and 22050 are shown in the below figure. For 40 mg capsules, batch 3317326 was used in study 22050 after a 2nd release testing as the batch was out of the previously assigned shelf-life of (b) (4) months (b) (4) and was required to be re-qualified for the bioavailability study. This batch was aged approximately 4 years at the time of use in study 22050. Batch 4366114 was aged approximately 6 months at the time of use in study 21665. As

shown by the in vitro dissolution profiles, the dissolution properties are essentially similar for both dose strengths 40 mg and 60 mg and also for the 40 mg batches after different storage time, which did not have impact on the in vitro dissolution properties.

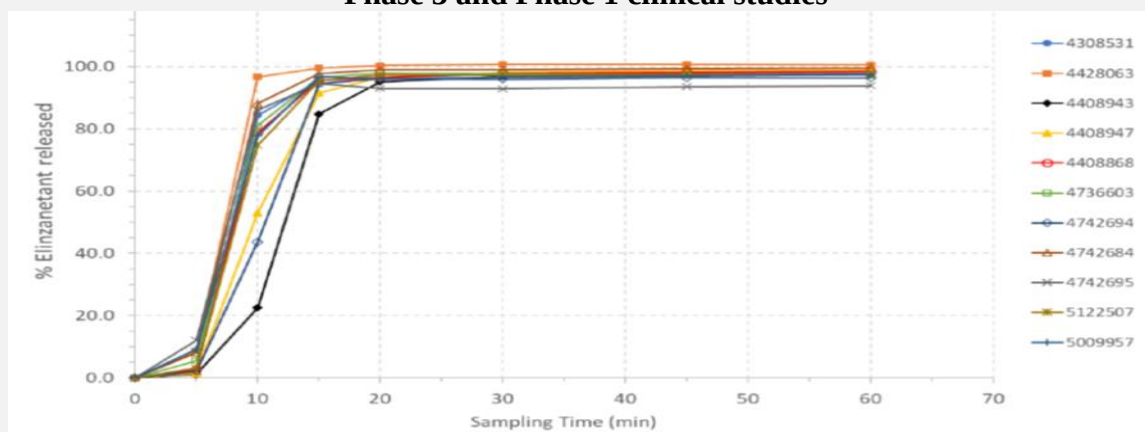
Figure 12: Dissolution profiles of 40 mg and 60 mg soft gel capsules used in relative bioavailability Phase 1, Phase 2b dose finding and other PK studies



Both clinical relative bioavailability studies 21665 and 22050 using the 40 mg dose strength (3 capsules) vs the 60 mg dose strength (2 capsules) at the 120 mg dose showed that both strengths showed comparable pharmacokinetic profiles and parameters (AUC, C_{max}) and thus were in agreement with the in-vitro dissolution results.

Elinzanetant 60 mg capsules have been used in several Phase 1 clinical studies as well as for the pivotal Phase 3 program. The in vitro dissolution profiles (Figure 13) from all batches of elinzanetant capsule 60 mg used in Phase 3 program (while some of these batches were also used in Phase 1 studies).

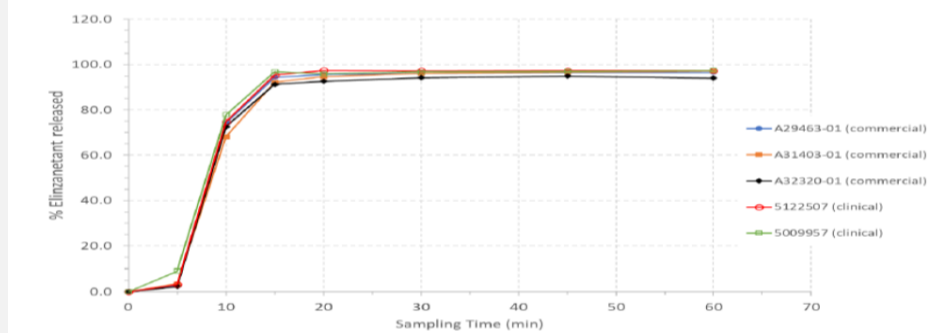
Figure 13: In vitro dissolution profiles of elinzanetant 60 mg soft gel capsule batches used in Phase 3 and Phase 1 clinical studies



Elinzanetant soft gel capsules – to-be-marketed product

Pivotal Phase 3 formulation and commercial formulations are same. Comparative in vitro dissolution of elinzanetant 60 mg soft gel capsules manufactured at the clinical site and batches manufactured at the final commercial site including scale-up demonstrate similarity as shown in the below figure.

Figure 14: Mean dissolution profiles of clinical and commercial batches



B. 13 BIOWAIVER REQUEST

Assessment: N/A

Biowaiver request is not applicable as the Applicant submitted only one strength for approval.

R. BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name: Kalpana Paudel, Ph.D.

Secondary Assessor Name: Tapash Ghosh, Ph.D.



Kalpana
Paudel

Digitally signed by Kalpana Paudel

Date: 3/13/2025 04:20:42PM

GUID: 562e1e15002f200f35c6ccac959cdb34



Tapash
Ghosh

Digitally signed by Tapash Ghosh

Date: 3/13/2025 04:24:43PM

GUID: 508da7230002a2433ddcef616ca190df

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
03/26/2025 10:37:30 AM