Date of Index Listing: June 24, 2025

FREEDOM OF INFORMATION SUMMARY

MODIFICATION OF A LISTING ON THE INDEX OF LEGALLY MARKETED UNAPPROVED NEW ANIMAL DRUGS FOR MINOR SPECIES

MIF 900-001

Ovaprim®

(salmon gonadotropin releasing hormone analog (sGnRHa) + domperidone)

Finfish broodstock

This modification provides for the addition of a new indication for use as a spawning aid in finfish broodstock.

Requested by:

Syndel USA

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	MIF 900-001
B. Requestor:	Syndel USA 1441 W Smith Road Ferndale, Washington
C. Proprietary Name:	Ovaprim®
D. Established Name:	salmon gonadotropin releasing hormone analog (sGnRHa) + domperidone
E. Pharmacological Category:	Spawning aid
F. Dosage Form:	Injectable Solution
G. Amount of Ingredient:	SGnRHa 20 µg/mL; domperidone 10 mg/mL
H. How Supplied:	10 mL glass vial (self-sealing); sterile liquid form
I. How Dispensed:	Over-the-Counter (OTC)
J. Dosage:	A general dose of Ovaprim® is 0.5 mL per kilogram of body weight. This dose may vary among species and water temperatures as addressed in the labeling.
K. Routes of Administration:	Intraperitoneal (intracoelomic) or intramuscular injection
L. Species/Class:	Finfish broodstock
M. Indication:	For use as a spawning aid in finfish broodstock

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY:

In accordance with 21 CFR part 516, a qualified expert panel evaluated the target animal safety and effectiveness of Ovaprim® for intraperitoneal or intramuscular injection for use as a spawning aid in finfish broodstock. FDA found the below qualified expert panel members acceptable as per 21 CFR 516.141(b)**.** The members of the qualified expert panel were:

- Roy P. E. Yanong, VMD (Panel leader)
- Matt DiMaggio, MS, PhD
- Shane Ramee, MS, PhD

A. Findings of the Qualified Expert Panel:

The qualified expert panel performed a comprehensive review of published literature and unpublished study data on salmon gonadotropin releasing hormone analog

(sGnRHa) and Ovaprim® in finfish species. Additionally, the qualified expert panel used anecdotal information and their own personal experience using the drug to complete their assessment of the target animal safety and effectiveness of Ovaprim® in finfish broodstock. Members of the qualified expert panel have had extensive experience using Ovaprim® in commercial and natural resource finfish production as well as in research applications (Pandey et al., 1998, Hill et al., 2009, DiMaggio et al., 2010, DiMaggio et al., 2013, DiMaggio et al., 2014, Broach et al., 2015, Siposetal, 2019, Siposetal, 2020; and others). According to the qualified expert panel, Ovaprim® has been used safely and effectively in commercial aquaculture for 35 years in over 40 countries. Ovaprim® has been listed in The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for intraperitoneal or intramuscular use as a spawning aid in ornamental finfish broodstock since March 17, 2009.

The qualified expert panel reviewed a total of 66 peer-reviewed published articles regarding the use of sGnRHa and Ovaprim® in finfish. Of the literature reviewed, 48 of the articles, which described use in 19 finfish species, were included in the assessment for the original request for addition to the Index for Ovaprim® (MIF 900-001, Freedom of Information Summary dated March 17, 2009) . To support the modification of the index listing for finfish broodstock, the qualified expert panel also reviewed an additional 18 articles evaluating target animal safety and effectiveness of sGnRHa in the following non-ornamental finfish species:

- Snow trout (*Schizothorax zarudnyi*) (Gharaei et al., 2011)
- African mudfish/catfish (*Clarias gariepinus*) (Achlonye-Nzeh and Obaroh, 2012; Ameer et al., 2021)
- Eurasian perch (*Perea fluviatilis*) (Kucharezyk et al., 2014)
- Grass carp (*Ctenopharyngodon idella*), rohu (*Labeo rohita*), mrigal carp (*Cirrhinus mrigala*), and silver carp (*Hypophthalmichthys molitrix*) (Ali et al., 2015)
- Pengba (*Osteobrama belangeri*) (Angel et al., 2015)
- Shirbot (*Barbus grypus*) (Ghami and Khodadadi, 2017)
- Northern pike (*Esox lucius*) (Cejko et al., 2018)
- African catfish (*Heterobranchus bidorsalis*) (Adubakar and Ipinjolu, 2019)
- Tambaqui (*Colossoma macropoma*) (Oliveira et al., 2023)
- Black sea bream (*Acanthopagrus berda*) (Abbas et al., 2019)
- Golden mahseer (*Tor putitora*) (Pandey et al., 1998)

Unpublished studies conducted under investigational use of sGnRHa showed that researchers collectively treated 5,000 fish across 28 different finfish species from 2017 through 2023. For the purposes of modifying the index listing, data generated from these studies supports the effectiveness and target animal safety of Ovaprim® in finfish broodstock. Adverse effects associated with the use of Ovaprim® primarily include redness at the site of injection and/or change in body color at the site of injection. This is consistent with the information reported in the Freedom of Information (FOI) Summary for the original request for addition to the Index dated March 17, 2009. In a 2009 study reviewed by the qualified expert panel, researchers adminstered a dose of Ovaprim® that was 4 times higher than the recommended dose included in the labeling to climbing perch (*Anabas testudineus*) (Bhattacharyya and Homechaudhuri, 2009). The results showed that the population of perch treated with the higher dose had high rates of ovulation and spermiation, yielding a high percentage of fertilization and hatching, but broodstock mortalities did occur in the study. As a result, the qualified expert panel advised using the recommended dose included in the labeling for Ovaprim®.

Based on a thorough review of published literature and unpublished data on the use of Ovaprim®, anecdotal information, and personal experience, the qualified expert panel came to a unanimous conclusion that the benefits of using Ovaprim®, for use as a spawning aid in finfish broodstock, outweigh the risks to the target animals.

B. Literature Considered by the Qualified Expert Panel:

The qualified expert panel reviewed the 48 articles included in the assessment for the original request for addition to the Index for Ovaprim® (MIF 900-001, FOI Summary dated March 17, 2009) along with the following 18 additional articles:

1. Abbas, G., Kasprzak, R., Malik, A., Ghaffar, A., Fatima, A., Hafeez-ur-Rehman, M., Kausar, R., Ayub, S. and Shuaib, N. 2019. Optimized spawning induction of blackfin sea bream, Acanthopagrus berda (Forsskal, 1775) in seawater ponds using Ovaprim® hormone, with general remarks about embryonic and larval development. Aquaculture, 512:734387.
2. Achionye-Nzeh, C.G. and Obaroh, I.S.R.A.E.L. 2012. Ovaprim® doses effects on eggs of African mudfish Clarias gariepinus. International Journal of Life Science and Pharma Research, 2(2): 6-9.
3. Abubakar M.Y. and Ipinjolu, J.K. 2019. Spawning Performance of Heterobranchus bidorsalis in Sokoto Dry Sub Humid Nigeria Using Ovaprim® C and Ovatide Hormones. Asian Journal of Emerging Research, 1(4): 141-153.
4. Ali, M.A., Rasheed, S.B., Zaigham Hassan, Z.H., Muhammad Ibrar, M.I., Abdul Majeed, A.M., Zafar Ulhaq, Z.U., Hamdullah Jan, H.J., Yahya Jan, Y.J., Abul Hasanat, A.H., Qureshi, M.S. and Hamid Khan, H.K. 2015. Efficacy of synthetic

hormones Ovatide and Ovaprim® in induced breeding of major Indian and Chinese carps. Journal of Agricultural Technology, 11(7): 1449-1456.

5. Ameer, M.W., Jabeen, F., Asad, M., Kaukab, G., Bashir, A., Rasheed, M., Younis, H., Munir, N., Nawaz, J., Zainab, R. and Akram, M. 2021. Comparative efficacy of Ovaprim® and hMG (menotropin) to induce breeding in African catfish {Clarias gariepinus). Fish Physiology and Biochemistry, 47(5): 1559-1564.

6. Angel, J.R.J., Tiwari, V.K., Babu, P.S., Rawat, K.D., Ignatius, B., Kiran, R.P., Roy, S., Charan, R., Nair, D.R., Rao, P.S. and Sreeramamurty, K.B. 2015. Captive breeding of a near threatened fish, pengba Osteobrama belangeri (Valenciennes, 1844) using three different inducing agents. Indian Journal of Fisheries, 62(4): 66-70.

7. Azevedo, P. de and Canale, L. 1938. A hipofise e sua agao nas gonadas dos peixes neotropicos. Arquivos do Instituto Biologico (San Paulo), 9:165-86. (as cited in Robertson and Rinfret, 1957).

8. Bhattacharyya, M., Homechaudhuri, S. 2009. Assessment of captive breeding of Anabas testudineus with the synthetic hormone, Ovaprim®. Proc Zool Soc 62, 23–27.

9. Broach, J.S., C.L. Ohs, M.A. DiMaggio, C.C. Green, and D.R. Yante. 2015. Efficacy of varying doses of pituitary extract from channel catfish, Ictalurus punctatus, on spawning performance of pinfish, Lagodon rhomboides, and pigfish, Orthopristis chrysoptera. North American Journal of Aquaculture, 77: 245-254.

10. Cejko, B.I., Krejszeff, S., Zarski, D., Judycka, S., Targohska, K. and Kucharczyk, D., 2018. Effect of carp pituitary homogenate (CPH) and sGnRHa (Ovaprim®) on northern pike (£sox lucius) spermiation stimulation and its effect on quantity and quality of sperm. Animal Reproduction Science, 193: 217-225.

11. DiMaggio, M.A., J.S. Broach, and C.L. Ohs. 2014. Evaluation of Ovaprim® and human chorionic gonadotropin doses on spawning induction and egg and larval quality of pigfish, Orthopristis chrysoptera. Journal of the World Aquaculture Society, 45: 243-257.

12. DiMaggio, M.A., J.S. Broach, and C.L. Ohs. 2013. Evaluation of Ovaprim® and human chorionic gonadotropin doses on spawning induction and egg and larval quality of pinfish, Lagodon rhomboides. Aquaculture, 414-415: 9-18.

13. DiMaggio, M.A., S.W. Grade, S.M. DeSantis, and C.L. Ohs. 2010. Induced volitional spawning and larval rearing of pinfish, Lagodon rhomboides. North American Journal of Aquaculture, 72: 252-257.

14. Gharaei, A., Rahdari, A. and Ghaffari, M., 2011. Induced spawning of Schizothorax zarudnyi (Cyprinidae) by using synthetic hormones (Ovaprim® and HCG). World Journal of Fish and Marine Sciences, 3(6): 518-522.

15. Kucharczyk, D., Targonska K., & Chwaluczyk R. 2014. Application of Ovaprim® in artificial reproduction of Eurasian perch, Perea fluviatilis L. under controlled conditions. Iranian Journal of Ichthyology, 1(1): 7-11.

16. Oliveira, R.G.S.D., Souza, G.B.D., Maria, A.N., de Freitas, R.A. and de Almeida, F.L., 2023. Effects of GnRH analogs on strip spawning and steroid plasma levels of Colossoma macropomum. Aquaculture International, 1-14.

17. Sipos, M.J., T.N. Lipscomb, A.L. Wood, S.W. Ramee, C.A. Watson, and M.A. DiMaggio. 2020. Evaluation of cGnRH lla for induction spawning of two ornamental Epalzeorhynchos species. Aquaculture Research, 51: 232-241.

18. Sipos, M.J., T.N. Lipscomb, A.L. Wood, S.W. Ramee, C.A. Watson, and M.A. DiMaggio. 2019. Evaluation of cGnRH lla for induction spawning of two ornamental Synodontis species. Aquaculture, 511: 734226.

III. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Ovaprim®:

Care should be taken to avoid accidental contact or self-injection. In the event of accidental self-injection, seek medical advice immediately. Use in a well ventilated area. Wear gloves, goggles and suitable protective clothing. Not for use in humans. Keep out of the reach of children.

Inhalation may be harmful. If breathing becomes difficult, move to fresh air, and contact a physician.

Ingestion may be harmful. If the person is conscious, wash out mouth with copious amounts of water and contact a physician.

Eye contact may be harmful. In case of eye contact, flush with copious amounts of water for at least 15 minutes. Assure adequate flushing by separating eyelids with fingers. Contact a physician.

Skin contact may be harmful. In case of skin contact, flush with copious amounts of water for at least 15 minutes. Remove contaminated clothing and wash before reusing. Contact a physician.

The toxicological properties of sGnRHa have not been thoroughly investigated. The actions are similar to luteinizing hormone releasing hormone (LHRH, Gonadotropin releasing hormone, GnRH) in humans. LHRH is the key mediator in the liberation of the pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). LHRH may modify reproductive ability by influencing plasma gonadotropin levels and concomitantly gonadal steroid levels.

IV. AGENCY CONCLUSIONS:

The information submitted in support of this request to modify the listing for Ovaprim® in the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) to add an indication for use as a spawning aid in finfish broodstock satisfies the requirements of section 572 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 516:

A. Determination of Eligibility for Indexing:

As part of the determination of eligibility for inclusion in the Index, FDA determined that the drug for this intended use was safe to the user, did not individually or cumulatively have a significant effect on the human environment, and that the description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of the new animal drug was sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture of the new animal drug. Additionally, the requestor has committed to manufacture the drug in accordance with current good manufacturing practices (CGMP).

The Index is only available for new animal drugs intended for use in minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals and for new animal drugs intended for use only in a hatchery, tank, pond, or other similar contained man-made structure in an early, non-food life stage of a food-producing minor species, where safety for humans is demonstrated in accordance with the standard of section 512(d) of the act. Some species of finfish are consumed by humans, so the use of Ovaprim® has been limited to broodstock finfish because FDA determined that there is a reasonable certainty that this population of finfish will not be consumed by humans or food-producing animals. Because this new animal drug is not intended for use in animals that will be used as food for humans or food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for granting this request to modify the index listing.

B. Qualified Expert Panel:

The qualified expert panel for Ovaprim® met the selection criteria listed in 21 CFR 516.141(b). The panel satisfactorily completed its responsibilities in accordance with 21 CFR part 516 in determining the target animal safety and effectiveness of Ovaprim® for use as a spawning aid in finfish broodstock.

C. Marketing Status:

In its written report, the qualified expert panel recommended that Ovaprim® be

available as an over-the-counter (OTC) product for this intended use. The Agency agrees that this product can be marketed OTC because the product labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

D. Exclusivity:

Products listed in the Index do not qualify for exclusive marketing rights.