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APPLICATION NUMBER:

208780Orig1s000

ENVIRONMENTAL ASSESSMENT

Environmental Analysis Update

Application: NDA 208780, Esbriet (pirfenidone) tablets (267 mg, 534 mg, and 801 mg strength)

Sponsor: Genentech, Inc.

Indication: Long-term treatment of idiopathic pulmonary fibrosis (IPF)

Reviewer: Jim Laurenson, OPQ/ONDP/Environmental Team

A. Summary

Genentech filed this NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The applicant submitted an environmental assessment (EA), based on an expected introduction concentration (EIC) of >1 ppb. The EA was reviewed by the drug product reviewer (DPR) and found to be acceptable for purposes of determining that approval of the application would not cause significant environmental impact. Subsequent to that review, the applicant provided additional information in response to an information request (IR). The new information confirmed the EA's and DPR's conclusion of no significant impact and also indicated that approval of the application either would not increase the use of the active ingredient, or if it did increase use, the EIC would be <1 ppb, such that a categorical exclusion from an EA would be relevant to either 21 CFR 25.31(a) or (b), respectively. The applicant's conclusions of no significant impact are consistent with a required statement of no extraordinary circumstances, pursuant to 21 CFR 25.15(a). Therefore, a categorical exclusion from an EA for this application is acceptable.

B. Background

Genentech filed NDA 208780 for Esbriet (pirfenidone) tablets (267 mg, 534 mg, and 801 mg strength) pursuant to section 505(b) of FFDCA, for the long-term treatment of IPF. The applicant submitted an EA, dated March 31, 2016, which indicated an EIC of (b) (4). The EA was reviewed by the drug product reviewer and found to be acceptable for purposes of determining that approval of the application would not cause significant environmental impact.

Subsequent to finalization of that review, FDA reviewed additional information provided by the applicant, dated October 5, 2016, in response to an earlier information request (IR). The IR, dated September 12, 2016, had noted that in the EA's Appendix D (Clinical Investigator's Brochure) and references, pirfenidone may cause sex hormone imbalance through release of hypothalamic dopamine, which in turn appears to reduce prolactin levels and alter the estradiol/progesterone ratio. This raised concern for hormonal effects in the environment, which is the subject of FDA's recently finalized environmental guidance related to drugs with potential estrogenic, androgenic, or thyroid activity (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf). FDA noted that while the lowest assessment factor (AF) of >8,000 noted in the EA was still substantial, this was based on OECD 210, fish early life stage test, which does not address several of the potential hormonal effects noted in the new FDA guidance. FDA subsequently conducted a fish plasma

model (FPM) analysis, per Huggett et al., 2003, as shown in the table below, which resulted in an AF (ER) of >14,000, also clearly substantial.

Fish Plasma Model (Huggett et al., 2003)					Comments
Input Data					
API	Pirfenidone				
NDA	208780				
Date Evaluated	9/7/2016				
Therapeutic concentration	14.7	ug/mL or mg/L			NDA 208870- pg. 65 EA
Log D at pH 7.0	0.9				NDA 208870- pg. 6 EA
MEEC	1.4	ug/L	ppb		NDA 208870- pg. 32 EA
Calculated Values for D_{lip} and $P_{b/w}$					
Log Dlip (Lipsome:water distribution coefficient)	1.0				QSAR of Tanoue et al., 2015
log $P_{b/w}$	-0.1				QSAR of Scott et al., 2016
$P_{b/w}$ (Water to plasma coefficient for fish)	0.7				
Effect Ratio					
ER	14126				< 1,000 = evaluate the need for further fish chronic exposure studies

This analysis used the EA's log P (log D) of 0.9, while FDA found predicted log Ps ranging from 1.69 (b) (4) (b) (4) to 2.14 (b) (4)

This latter log P would result in an AF (ER) closer to 1,000, the lower limit recommended by Huggett et al. (2003) to account for uncertainties in the model. Therefore, the applicant was asked to confirm the source of the log P (log D) of 0.9. The applicant also was asked to provide a literature search and discussion of any additional information that could elucidate the potential for environmental effects, such as from adverse outcome pathway/mechanistic data, other dopamine agonists that could be used for "read across" and cumulative risk purposes, and data on metabolism, fate, and transport that can be used to refine environmental concentration estimates and risk characterization.

C. Additional Information from Applicant

The applicant's IR response addressed the question about whether pirfenidone may cause sex hormone imbalance through release of hypothalamic dopamine, which in turn appears to reduce prolactin levels and alter the estradiol/progesterone ratio, by noting that the risk of inhibition by pirfenidone was considered to be a rat-specific contributor to chronic tumor risk observed in that study only, and considered negligible for other mammal species (including humans). Similarly, the applicant was unable to define a plausible pharmacokinetic aquatic toxicity risk related to prolactin inhibition in fish or amphibians.

The applicant also updated their production volume to below (b) (4), which transforms into an EIC of <1 ppb, and noted again that pirfenidone is rapidly metabolized and the byproducts are environmentally inert.

Regarding the octanol/water partition coefficient, the applicant noted that independent experiments by others found log P values of 0.9 and 1.06, and that the quantitative structure-activity relationship (QSAR) predicted values are based on a series of structures that are different from pirfenidone (i.e., fused arylpyridones and indoles instead of N-arylpyridones), which can explain the large gap between predicted and experimental log D values. The applicant therefore concludes that the maximal QSAR value of 2.14 is neither applicable for pirfenidone nor a reliable starting point for deriving fish plasma concentrations. Furthermore, the measured solubility profile of pirfenidone in water remains unchanged over a large range of pH values (pH 1 - 10), and therefore it is not expected that the log D values at various pH values would be much different from the log P value.

The applicant was unable to find new literature information as to environmental properties (biodegradation, environmental fate, ecotoxicological effects or monitoring data) for pirfenidone.

D. Review of Additional Information

FDA has identified recent research acknowledging that while it currently is not known whether mechanisms causing sex hormone imbalance in rats from the release of hypothalamic dopamine are conserved across vertebrate species, some recent evidence of these effects in aquatic organisms exists (Bryant et al., 2016). The data are limited and preliminary, however, and do not necessarily indicate population effects. Furthermore, FDA agrees that the lower log P values are reasonable for the fish plasma model, and thus the ER of >14,000 indicates the EIC likely is substantially lower than aquatic concentrations that would pose a risk, especially after factoring in the metabolism, dilution, and degradation.

The new data indicating that the EIC is <1 ppb indicates that a categorical exclusion from an EA based on 21 CFR 25.31(b) is applicable. In addition, a reference in the EA to a categorical exclusion based on 21 CFR 25.31(a), which is for applications that do not increase the use of the active ingredient, also is applicable. Furthermore, the applicant's conclusions of no significant impact are consistent with a required statement of no extraordinary circumstances, pursuant to 21 CFR 25.15(a).

E. Conclusions

The new information from the applicant confirmed the EA's and DPR's conclusion of no significant impact and also indicated that approval of the application either would not increase the use of the active ingredient, or if it did increase use, the EIC would be <1 ppb. Thus, a categorical exclusion from an EA, pursuant to either 21 CFR 25.31(a) or (b), is relevant. The applicant's conclusions of no significant impact are consistent with a required statement of no extraordinary circumstances, pursuant to 21 CFR 25.15(a). Therefore, a categorical exclusion from an EA for this application is acceptable.

E. References

Bryant, A. S., Greenwood, A. K., Juntti, S. A., Byrne, A. E., & Fernald, R. D. (2016). Dopaminergic inhibition of gonadotropin-releasing hormone neurons in the cichlid fish, Astatotilapia burtoni. Journal of Experimental Biology, jeb-147637.

Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal 9(7): 1789-1799.

Scott, W. C., Du, B., Haddad, S. P., Breed, C. S., Saari, G. N., Kelly, M., ... & Brooks, B. W. (2016). Predicted and observed therapeutic dose exceedances of ionizable pharmaceuticals in fish plasma from urban coastal systems. Environmental Toxicology and Chemistry, 35(4), 983-995.

Tanoue, R., Nomiyama, K., Nakamura, H., Kim, J. W., Isobe, T., Shinohara, R., ... & Tanabe, S. (2015). Uptake and tissue distribution of pharmaceuticals and personal care products in wild fish from treated-wastewater-impacted streams. Environmental science & technology, 49(19), 11649-11658. doi: 10.1021/acs.est.5b02478

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