NIOSH Reevaluation of Liraglutide on the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings

October 3, 2023

Executive Summary

Recommendation

NIOSH recommends that liraglutide be removed from the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* (the *List*) [NIOSH, 2016]. Liraglutide does not meet the NIOSH definition of a hazardous drug for healthcare workers because the hazards of concern—mitogenic carcinogenicity and developmental toxicities—are expected to require sustained levels of systemic exposures to cause an adverse effect, and the intrinsic properties of liraglutide mean relevant sustained systemic exposure levels are unlikely.

Summary

NIOSH received a request from the manufacturer of liraglutide to reevaluate the placement of liraglutide on the *NIOSH List of Antineoplastics and other Hazardous Drugs* (the *List*), 2016. Based on evidence from the prescribing information, liraglutide has been shown to cause specific C-cell related thyroid tumors and developmental effects in rodents [FDA 2009]. Because of this liraglutide was determined to meet the NIOSH definition of a hazardous drug and added to the *List* in 2014. Liraglutide was placed on Table 2, *Non-antineoplastic drugs that meet one or more of the NIOSH criteria for a hazardous drug, including those with the manufacturer's safe-handling guidance (MSHG).* Supplemental information included a Black Box warning for thyroid C-cell tumors and a designation as a Food and Drug Administration (FDA) Pregnancy Category C drug.

The manufacturer noted in their request that "liraglutide is only licensed and prescribed to be administered via a sealed, pre-filled, injectable pen; therefore, the occupational exposure risk due to transport, administration and dispensing to a healthcare worker is minimal at worst, and practically non-existent. Liraglutide pens are shipped in individually boxed containers, and a pharmacist's interaction is typically limited to affixing the printed prescription label on the boxed container before providing the medication to the patient." The *List* identifies potentially hazardous products that are handled in healthcare workplaces. It does not assess the risk posed by handling specific market formulations or products, as these may change over time**. NIOSH does not undertake a full risk assessment of all the drugs that are placed on the *List*. Therefore, NIOSH has not considered the specific way that a manufacturer sells, ships, dispenses, or administers their product as part of the evaluation of the molecule's potential hazard in the workplace.**

The manufacturer also provided additional information on bioavailability via routes of exposure that are of occupational interest. These data reflect intrinsic properties of the molecule that affect the potential hazard it poses while being handled in healthcare settings. Bioavailability affects the systemic exposure

potential of a drug and therefore affects the risk of exposure to the drug. However, because bioavailability is an intrinsic property of the molecule, it also affects the hazard posed by all potential formulations in all handling situations. In the *Procedures for Developing the NIOSH List of Hazardous Drugs,* NIOSH has included criteria for the consideration of molecular properties (section V C.4) that may limit the potential mechanism of toxicity and therefore the potential to cause adverse health effects by routes of exposure relevant to healthcare workplaces [NIOSH, 2023]. In this reevaluation NIOSH documents the determination of the potential hazards posed by liraglutide, taking into account the newly available data on how those hazards may be affected by bioavailability.

In their request for reevaluation the manufacturer stated that the mechanism of action that led to the formation of thyroid tumors in rodents was not relevant to humans [FDA 2009]. They also stated that the developmental issues seen in animal studies were secondary to maternal decreased food intake and therefore also not relevant to humans. NIOSH has determined that the carcinogenic hazard posed by liraglutide is likely via a mitogenic[1] mode of action, requiring consistent long-term systemic exposure (see Carcinogenicity section below). NIOSH also found that it is unlikely that the developmental toxicity is related exclusively to decreased maternal food intake because in addition to decreased pup size, there is increased fetal death and fetal malformations (see Developmental Toxicities section below). The available data show that systemic bioavailability of liraglutide via the oral and inhalation routes of exposure in rats and beagle dogs is less than 0.1% [Sauter et al., 2019; Uhl et al., 2020]. The bioavailability via inhalation is between 0.6% and 1.7% in cynomolgus monkeys [Nordisk, 2020] and was less than 0.1% in beagle dogs [Sauter et al., 2019]. This evidence indicates that inhalation and ingestion exposure to liraglutide in an occupational setting are unlikely to result in high enough doses to cause the carcinogenic or developmental effects observed in laboratory studies. Similarly, the skin serves as a highly limiting barrier to the systemic bioavailability of peptides like liraglutide and dermal absorption is not likely to be an important route of systemic exposure for liraglutide in healthcare settings. Occupational exposure to liraglutide is possible from sharps injuries such as needlesticks. However, in most healthcare workplaces needlestick injuries are rare, and not likely to produce the long-term subcutaneous exposure which would be needed for the observed toxicity in laboratory animals. Occasional occupational exposure by dermal, oral, or inhalation routes may occur. However, these exposures are unlikely to result in significant systemic exposures due to the low level of systemic bioavailability for liraglutide via these routes.

Based on its reevaluation, NIOSH determined that due to the intrinsic properties of the molecule and the anticipated routes of exposure in a healthcare workplace, systemic bioavailability in healthcare workers necessary for the carcinogenic or developmental effects observed in laboratory animals are highly unlikely.

Toxicity Evaluation

Carcinogenicity

A black box notification on the prescribing information for liraglutide states that it causes thyroid C-cell tumors at clinically relevant exposures in mice and rats. Increased cellular proliferation and tumors were

[1] Mitogenic molecules are molecules that stimulate cell growth. Sustained exposure is typically required for mitogens to cause adverse health effects. Short-term exposure to mitogens causes transient cell proliferation which is reversible after the end of exposure.

reported in both sexes in both species. Increased proliferation of thyroid C-cell tumors was not reported in cynomolgus monkeys. The manufacturer suggested that the proliferation of tumors in mice and rats is due to higher glucagon-like peptide-1 receptor (GLP-1R) expression in rodents than in primates. This higher GLP-1R expression in rodents leads to an increased level of plasma calcitonin, a marker of C-cell activity, with treatment. No increase in calcitonin plasma levels was seen in cynomolgus monkeys, and no thyroid C-cell tumors were noted. The manufacturer stated that in GLP-1R knock-out mice there was no C-cell proliferation. In humans, C-cell thyroid cancers, known as medullary thyroid carcinoma (MTC), are rare and most are related to mutations in a proto-oncogene called **RE**arranged during **T**ransfection (RET). In familial MTC, hyperplasia and increased plasma calcitonin levels (hypercalcitoninemia), and related increases in plasma calcium, precede carcinoma.

The manufacturer's submission to the FDA proposed a mechanism of action in rodents in which circulating systemic liraglutide binds to and activates GLP-1Rs on C-cells, which induces calcitonin release from the C-cells, leading to increased calcitonin synthesis. This persistent C-cell stimulation leads to C-cell hyperplasia in rodents, which over time leads to C-cell neoplasia [FDA, 2009].

The FDA decided that the weight of evidence was not sufficient to support the manufacturer's proposed mechanism of action. FDA noted that in rodents liraglutide increased focal hyperplasia, which is a preneoplastic lesion, not diffuse hyperplasia. The FDA stated diffuse hyperplasia would be the expected physiologic response to liraglutide in rodents, given that there was insufficient evidence to conclude that in the thyroid the GLP-1R was localized specifically to C-cells. The FDA also noted that in rats liraglutide increased the progression of age-related focal C-cell hyperplasia to adenomas and carcinomas but did not actually increase the rate of focal C-cell hyperplasia. Liraglutide did not cause sustained dose-related increases in plasma calcitonin above normal rat age-related increases, despite higher incidences of C-cell neoplasia, indicating that plasma calcitonin levels are not a marker of thyroid C-cell neoplasia in rats. The FDA stated that the carcinogenicity studies in rats for liraglutide (and the related GLP-1 like polypeptide drug exenatide) indicated that persistent GLP-1R activation led to C-cell neoplasia in rats. However, the precise role of the GLP-1R activation in mediating those liraglutide-induced thyroid tumors is unknown [FDA, 2009].

Since the data for rodents were insufficient to show the thyroid C-cell GLP-1R specific mechanism of action for C-cell hyperplasia progression to adenoma and carcinoma, the higher levels of GLP-1R in rodents do not rule out the relevance of liraglutide-related increases in thyroid C-cell neoplasia progression for humans. Therefore, the relevance of C-cell neoplasia progression in response to liraglutide in humans is not known. However, the liraglutide-related C-cell neoplasia appears to involve a mitogenic mechanism of action, related to long-term continued activation of the GLP-1R by long-acting GLP-1R agonist drugs. NIOSH considered this mechanism of action in its reevaluation of the potential occupational hazard of liraglutide.

Developmental Toxicity

The prescribing information for liraglutide notes its potential toxicities as causing decreased pup weight, fetal malformations, and increased fetal death in animal studies. In rats, doses as low as 0.8 times the maximum recommended human dose (Area Under the Curve comparison) that began 2 weeks before mating and continued through gestation day 17 led to abnormalities in kidney and blood vessel development and irregular ossification of the skull. In rats treated with similar doses on gestational day

6 through weaning, parturition was delayed, and the group mean weight of treated neonatal rats was lower than the control. Similarly, liraglutide treatment of rabbits on gestational day 6 through day 18 led to decreased fetal weight. In the same study dose dependent increase in fetal malformations at all tested doses were reported, including malformations of the kidneys, scapula, eyes, and forelimbs observed at the lowest noted doses.

The manufacturer posited that the observed developmental effects were due to decreased maternal food intake, resulting in decreased maternal weight. However, while decreased fetal weight may be explained by a decrease in maternal food intake, the other dose-dependent fetal abnormalities are less likely to be associated with maternal food restriction and weight loss. Therefore, NIOSH concluded that a decrease in maternal food intake only partially explains the observed developmental adverse health effects.

Integrated Toxicity and Molecular Property Hazard Characterization

Dermal

Liraglutide is a 3.751 kDa peptide. Dermal absorption of peptides is generally very low without additional chemical or physical disruption of the skin's natural barrier. Significant liraglutide penetration is unlikely to occur through intact skin in typical occupational exposure scenarios [Bos and Meinardi, 2000; Courtenay et al., 2018]. For skin that is not intact, liraglutide reaching systemic bioavailability is possible; however, less than the full recommended therapeutic dose is likely to reach the subcutaneous layer in an occupational exposure to broken skin. Because liraglutide is slowly absorbed, reaching C_{max} between 9 and 12 hours, single low-level exposures significantly below the therapeutic dose are unlikely to lead to high systemic exposure levels. In occupational settings, systemic bioavailability is unlikely to reach the same level as subcutaneous injection, and unintentional exposure is unlikely to be repeated on a regular basis in even the worst-case occupational situations. Therefore, dermal exposure to liraglutide in the workplace is unlikely to represent a significant source of hazard.

Inhalation

The manufacturer stated that in their studies systemic bioavailability via inhalation in cynomolgus monkeys was between 0.6% and 1.7% [Nordisk, 2020]. In beagle dogs inhalation exposure led to less than 0.1% total bioavailability [Sauter et al., 2019]. These findings indicate that inhalation exposure to liraglutide in the workplace is not likely to result in sufficient regular systemic bioavailability to cause the adverse health effects described above.

Oral

Oral bioavailability for most peptides, including GLP-1 agonist peptides, is low because peptides are broken down in the gastrointestinal system [Hamman et al., 2005; He et al., 2019; Sauter et al., 2019; Uhl et al., 2020]. This is also true of liraglutide. Studies investigating ways to increase liraglutide oral bioavailability have shown bioavailability by this route to be low. In a study in rats, less than 0.25% of the radiolabeled liraglutide was found in the blood plasma after oral administration, while in beagle dogs, total bioavailability was less than 0.01% via oral administration [Sauter et al., 2019; Uhl et al., 2020]. Therefore, oral occupational exposures are unlikely to result in sufficient regular systemic levels of liraglutide to cause the adverse effects described above. Occupational oral exposures would most likely be due to contamination transfer via hand to mouth.

Discussion

Evaluation of the potential hazards of liraglutide indicates liraglutide can cause tumors in the thyroids of rodents. The potential mechanism of this carcinogenicity, mitogenic activity related to GLP-1R activity in thyroid C-cells does not rule out it being potentially relevant in some workers. Additionally, observed developmental effects, including malformations of the kidneys, scapula, eyes, and forelimbs observed at the lowest noted doses, cannot be attributed to solely decreased maternal food intake on the available data alone, and may be a relevant hazard to workers who are pregnant or wanting to become pregnant. However, characterization of the hazard of the liraglutide also indicates that, given the low bioavailability of the liraglutide peptide via relevant workplace exposure routes, the hazard to healthcare workers exposed to liraglutide in the workplace is low. Exposure via dermal, inhalation, or oral routes to the liraglutide peptide in healthcare workplaces are unlikely to lead to systemic levels that are necessary to cause the developmental effects noted in rodents or to maintain the C-cell mitogenic effects needed to lead to thyroid cancers. Therefore, despite potentially posing a developmental or carcinogenic hazard, that hazard is not likely to be relevant in workplace exposure scenarios and NIOSH should remove liraglutide from the NIOSH *List*.

References

Bos JD, Meinardi MMHM [2000]. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exper Dermol *9*(3):165–69. https://doi.org/10.1034/j.1600-0625.2000.009003165.x

Courtenay AJ, McCrudden MTC, McAvoy KJ, McCarthy HO, Donnelly RF [2018]. Microneedle-mediated transdermal delivery of bevacizumab. Mol Pharm *15*(8):3545–56. https://doi.org/10.1021/acs.molpharmaceut.8b00544

FDA [2009]. Liraglutide Pharmacology Review. Retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/

Hamman JH, Enslin GM, Kotze AF [2005]. Oral delivery of peptide drugs: barriers and developments. BioDrugs *19*(3):165–77. https://doi.org/10.2165/00063030-200519030-00003

He S, Liu Z, Xu D [2019]. Advance in oral delivery systems for therapeutic protein. J Drug Target *27*(3): 283–91. https://doi.org/10.1080/1061186x.2018.1486406

NIOSH [2016]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication Number 2016–161 (Supersedes 2014–13). https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf

NIOSH [2023]. Procedures for developing the NIOSH list of hazardous drugs in healthcare settings. By Whittaker C, Ovesen JL, MacKenzie BA, Hartley T, Berry KA, Piacentino J. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2023-129

Novo Nordisk [2020]. Liraglutide NNC 0090-1170 Health classification and occupational exposure limit. Provided by Novo Nordisk.

Sauter M, Uhl P, Majewsky M, Fresnais M, Haefeli WE, Burhenne J [2019]. An ultrasensitive UPLC–MS/MS assay for the quantification of the therapeutic peptide liraglutide in plasma to assess the oral and nasal bioavailability in beagle dogs. Bioanalysis, *11*(9):887–98. https://doi.org/10.4155/bio-2018-0322

Uhl P, Grundmann C, Sauter M, Storck P, Tursch A, Ozbek S, Leotta K, Roth R, Witzigmann D, Kulkarni JA, Fidelj V, Kleist C, Cullis PR, Fricker G, Mier W [2020]. Coating of PLA-nanoparticles with cyclic, arginine-rich cell penetrating peptides enables oral delivery of liraglutide. Nanomedicine *24*:102132. https://doi.org/10.1016/j.nano.2019.102132