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HEALTH IMPACT EVALUATION
rusty needle confirmed 0.4 % NaCl diluent for Act-Hib®

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SUMMARY:

An investigation was conducted following product technical complaints (PTC) received on an Act-Hib® vaccine from customers in Japan who had observed oxidation present at the external and/or internal surface of the needle (16 mm, 25 G) of the 0.4% NaCl diluent syringe (fixed needle type) used for the reconstitution and injection of Act-Hib®. For the affected needles, 2 types of oxidation defects have been identified: either the presence of an oxidation spot on the external surface of the needle or, alternatively, oxidation on the internal surface of the needle presenting as a brownish stain at the tip/base of the syringe needle. Analytical investigations identified iron oxide/hydroxide in the oxidation material. The investigation concluded that the rate of potential oxidation of the needle is extremely rare (oxidation defect rate is estimated at 0.03% with a confidence limit of 95% meaning between 0.01% and 0.07% per 0.4%NaCl diluent batch).

Even if oxidation has been reported only in the absence of vaccine injection, and if visual inspection before reconstitution present a significant probability to detect these rare defects (in which case the defected syringe would be discarded), an assessment of the potential toxicological risk related to the presence of iron oxide and/or iron hydroxide was done based on both animal toxicology data and clinical data. A comprehensive literature search was conducted to identify scientific publications with special focus on risk of exposure to iron oxide/hydroxide via subcutaneous or other parenteral routes.

Assessment of particles

The risk assessment took into consideration potential impact depending on size, amount, and nature of iron oxide/hydroxide particles. In the present situation, no iron oxide/hydroxide particles have been identified from the needles and no events suggesting injection of particles have been reported. Nevertheless, the risk assessment included two hypothetical scenarios: the risk for local effects related to injection of large-sized particles (larger than 4-10 μm), and the risk for systemic effects related to injection of small-sized particles (less than 4 μm).

Studies have shown that when injected intramuscularly or subcutaneously (as is the case with Act-Hib®), large non-biodegradable particles tend to remain locally in the injected tissue, where they are taken up by local immune cells (macrophages or giant cells), or may be encapsulated in connective tissues.[i,ii] There may be an inflammatory response at the injection site, consistent with

a normal foreign body reaction to non-toxic, non-biodegradable particles, with no evidence of systemic effects being observed.[iii] Further, a review of worldwide vaccinology literature, accumulated since the early 1940s, showed no published reports of vaccine injection site granulomas or nodules caused by intramuscular injection of particles of metal origin or of any other origin.[iv] It is important to remember that (1) the impacted needles are indicated for single use via subcutaneous route; (2) vaccinees will be exposed for a very short period of time, and the needle may not be in place long enough to elicit an inflammatory response to iron oxide/hydroxide; (3) despite in the event some of the oxidation particles detach from the needle and remain deposited at the injection site, the likelihood for the vaccinee to develop a clinical reaction remains very low based on the limited quantity of iron oxide/hydroxide particles that might be deposited at the injection site. Thus, in the event that an oxidized needle is used, any inadvertent inoculation of large particles may enhance the slight inflammatory reactions usually seen following Act-Hib® vaccination at the injection site.

In the other scenario, if small particles (nanoparticles) were injected, these might migrate systemically and be distributed to organs distant from the injection site. The results of the analytical investigation of the affected needles and calculations of a hypothetical scenario which administered possible maximum dosage of iron oxide or iron hydroxide showed that the risk of any toxic impact is very low in view of the limited number of particles and the very low overall theoretical maximum dose of iron oxide or hydroxide that could potentially be injected.

Toxicological assessment

Further, a literature review of toxicological data in animals and humans on iron oxide or iron hydroxide was conducted. Concerning data in animals, the studies identified were mainly investigative, but these are reassuring in that no major safety concern is expected following iron oxide injection.[v,vi,vii] The dose-levels used were far above the potential amount of iron oxide that could be injected in the current situation. In humans, iron oxide has been used for various pharmaceutical and non-pharmaceutical purposes, such as food colorants and pharmaceutical excipients without any safety concerns.[viii,ix,x,xi] In addition, Ferumoxytol (Feraheme®) (iron oxide in form of Fe_3O_4), is administered as an intravenous infusion for the treatment of iron deficiency anemia in adults suffering from chronic kidney disease. From these and other data, it can be concluded that iron oxide has a low intrinsic toxicity profile after one single administration. This treatment was approved in 2009 by the Food and Drug Administration (FDA) and in 2012 by the European Medicines Agency (EMA) as a treatment to be administered intravenously.

There is limited information regarding iron hydroxide either as a chemical entity or particle. The most relevant data come from treatment of iron deficiency (anemia) in humans, for which injectable iron, in the form of ferric hydroxide solutions, are marketed overseas. Venofer® (age indication from 2 years onwards) is used at a dose of 0.5mg/kg.[xii, xiii] Theoretically, in a 3.5-kg baby, this would represent a dose of 1.75mg iron, which corresponds to 47 mg of the [iron hydroxide-sucrose] complex, which is far above the potential exposure level in the present case. In addition, this dosing regimen may be repeated every 2 weeks or every 4 weeks for 12 weeks, while in the present case, potential exposure to iron hydroxide would be on one single occasion. Another injectable solution of ferric hydroxide in form of a dextran complex has been approved by FDA for intramuscular or intravenous treatment of anemia: Ferrisat®. 1 mL-Ferrisat® contains 50 mg of iron and 312.5 mg of [iron hydroxide-dextran] complex, and may be injected to treat

anemia.[xiv,xv] Therefore, these data are considered to confirm the absence of safety risk related to potential injection of a very low quantity of iron hydroxide.

Safety Assessment

Finally, a medical review of the safety reports received from Japan regarding the affected products was also performed. No new or significant safety concerns were identified, and no safety signal or risk was evidenced. No association with the potential presence of iron oxide or iron hydroxide on the needle is suspected. From this overall review there is no evidence that the safety profile of the concerned vaccine has changed over time.

Immune responses following immunization

Regarding the impact on the immunogenicity of a product with presence of oxidation on the needle, there is no clinical reason to anticipate a decrease of the immune responses following immunization. Based on this, it is considered that there is no need to revaccinate children who may have received at least one dose of the concerned product.

Thus, based on the nature of the event, the very low rate of oxidation in the needles, the review of the available literature, and the analysis of the toxicological and pharmacovigilance data, it is possible to conclude that the presence of the iron oxide/hydroxide particles is not expected to cause substantial adverse effects. While HCPs are advised not to use a needle with any observed oxidation, if injected subcutaneously in humans this might, in the worst-case scenario, be associated with a slightly increased rate, severity and/or duration of injection-site adverse reactions. To date, the safety reports from the batches on the market do not suggest any new or significant safety concerns.

Therefore, the benefit / risk ratio of the impacted Act-Hib® batches remains positive, particularly when considering a scenario of product shortage and interruption of the Hib vaccination program in Japan.

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[i] Lemperle G, Morhenn MD, Pestonjamasp V, Gallo RL. Migration studies and histology of injectable microspheres of different sizes in mice. Plastic Reconstructive Surgery. 2004; 13(5): 1380-1390

[ii] Fellah BH, Josselin N. Inflammatory reaction in rats muscle after implantation of biphasic calcium phosphate microparticles. Journal of Material Science: Materials in Medicine. 2007; 18: 287-294

[iii] Moore RJ, Vernon-Roberts B, Blumbergs PC, Hutchens MJ, Kamat AS and Koszyca B. The biologic response to particles from a lumbar disc prosthesis. Spine. 2002; 27(19): 2088-2094

[iv] Doessegger L & al. The potential clinical relevance of visible particles in parenteral drugs. J Pharm Sci 2012; 101: 2635-2644

[v] UCLID Dataset, European Commission, 18 Feb. 2000, diiron trioxide, CAS 1309-37-1

[vi] Askri & al. Sub-acute intravenous exposure to Fe2O3 nanoparticles does not alter cognitive performances and catecholamine levels, but slightly disrupts plasma iron level and brain iron content in rats. Journal of Trace Elements in Medicine and Biology. 50 (2018) 73 79.

[vii] Yun JW & al. The toxicity and distribution of iron oxide-zinc oxide core-shell nanoparticles in C57BL/6 mice after repeated subcutaneous administration. J Appl Toxicol. 2015 Jun;35(6):593-602. doi: 10.1002/jat.3102

[viii] FAO/WHO JECFA. Evaluation of some food additives. 1980;23(648).

[ix] FDA/ Center for Food Safety & Applied Nutrition. Summary of color additives listed for use in the US. 2007.

[x] Scientific Opinion on the re-evaluation of iron oxides and hydroxides (E 172) as food additives EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). 2015. Scientific Opinion on the re-evaluation of iron oxides and hydroxides (E 172) as food additives. EFSA Journal 2015;13(12):4317, 57 pp. doi:10.2903/j.efsa.2015.4317 Available online: www.efsa.europa.eu/efsajournal

[xi] Scientific opinion from EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). Adopted: 21 April 2016. doi: 10.2903/j.efsa.2016.4482. Safety and efficacy of iron oxide black, red and yellow for all animal species.

[xii] VENOFER. Summary of Product Characteristics. http://base-donneespublique. medicaments.gouv.fr/affichageDoc.php?specid=60080232&typedoc=R last access February 5th, 2020

[xiii]https://www.venofer.com/ - last access on February 5th, 2020

[xiv] FERRISAT. Summary of Product Characteristics. http://base-donneespublique. medicaments.gouv.fr/affichageDoc.php?specid=64392350&typedoc=R last access February 5th, 2020

[xv] https://pillintrip.com/medicine/ferrisat - last access on February 5th, 2020