

Langen, 23 December 2020

## NOTIFICATION

### RECOMMENDATION ON CORONA VACCINATION FOR ALLERGIC PERSONS

Based on reports in the media, two cases of serious putatively allergic adverse events were observed in the United Kingdom (UK) in connection with the vaccination campaign with the RNA based vaccine BNT162b2 from BioNTech/Pfizer. This vaccination campaign has been carried out in the UK since 8 December 2020. The British Medicines and Healthcare Products Regulatory Agency (MHRA) has already made a statement concerning these reports on 9 December 2020 [1]: “A person with a history of anaphylaxis to a vaccine, medicine or a food product should not receive the vaccine by Pfizer/BioNTech. A second dose should not be given to anyone who has experienced anaphylaxis following administration of the first dose of this vaccine.”

The experts for allergy and pharmacovigilance of the Paul-Ehrlich-Institut have reviewed the data available from clinical trials and the European register for spontaneous reports with regard to possible recommendations for persons with allergies concerning vaccines for the protection from COVID-19.

#### 1. Data from clinical studies with the BNT162b2 vaccine

The publicly accessible MHRA Public Assessment Report - Authorisation for Temporary Supply COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA) concentrate for solution for injection (as per 11 December 2020) [2] indicates that in Phase 2/3 studies with the BNT162b2 vaccine, in which 21,621 persons received the vaccine (verum) and 21,631 received placebo, serious adverse effects in general occurred in 111 persons (0.5 percent) of the placebo group and in 126 persons (0.6 percent) in the verum group, out of which, with four reactions in the verum group, a connection to the vaccine was seen by the study doctors (versus 0 in the placebo group).



In the organ-specific observation (System Organ Class, SOC) of all adverse effects, with n=5.770 (26.7 percent) in the verum group and n=2638 (12.2 percent) in the placebo group, 26 (0.1 percent) adverse reactions of the SOC “Immune system disorders” are documented in the verum group compared with 22 (0.1 percent) in the placebo group.

Within the SOC of immune system disorders, six participants reported drug hypersensitivity after BNT162b2 compared to one after placebo. One participant reported drug hypersensitivity and urticaria on the day of dose 1 of BNT162b2; both events were of moderate severity and lasted one day. Another participant reported a drug hypersensitivity event 23 days after Dose 1 of BNT162b2. The five other drug hypersensitivity events were documented by investigators as reactions to other drugs. Five participants reported Immunisation reactions after BNT162b2 compared to none after placebo; all were associated with other systemic reactogenicity events and none was associated with events that would indicate hypersensitivity

Immediate adverse effects (within 30 minutes after administration) were reported by 101 (0.5 percent) participants after dose 1 of the administration of BNT162b2 compared with 77 (0.4 percent) after the administration of placebo. Immediate adverse reactions after dose 2 were reported by 57 (0.3 percent) of the participants after BNT162b2 vs. 46 (0.2 percent) after administration of placebo. The predominant immediate event was injection site pain. No participant reported an immediate allergic reaction after either dose of BNT162b2.

In both the above-mentioned studies, subjects with a serious adverse reaction in connection with a vaccine and/or a serious allergic reaction (e.g. an anaphylactic reaction) to a component of the study medication in their history were excluded from the study. The assessment report indicates that post-authorisation monitoring for hypersensitivity events will be conducted.

## **Conclusion**

Since in the above-mentioned studies, subjects with a serious adverse reaction in connection with a vaccine and/or a serious allergic reaction (e.g. anaphylaxis) to a component of the study medication in their history were excluded from the study, no clinical data are available on the tolerability and safety of the vaccine for this group of persons.

The study protocol did not exclude individuals with non-severe allergic reactions to other vaccines or individuals with an allergic reaction, of any severity, to medication, food or environmental allergies. There is no evidence from the assessment report referenced that this group of persons has an increased risk of adverse effects. A targeted subgroup analysis of treated persons who have allergic underlying diseases cannot be derived from the above-mentioned public assessment report of 11 December 2020 (yet). The publication of the subgroup analysis performed in the meantime by the manufacturer is expected in a timely manner.

## **2. Information from the European register of spontaneous reports: Evidence on the capture and assessment of risks**

The experts for allergies and pharmacovigilance at the Paul-Ehrlich-Institut have reviewed the above-mentioned cases as well as others which have been reported ever since in the European register for spontaneous reports. The spontaneous capture of adverse effects performed up to now in connection with a vaccination for the protection from COVID-19 with the BNT162b2 vaccination frequently lacks case-related information which is required to narrow down risk factors and risk groups. Such information includes:

- Indication of the allergic symptoms which occurred in concrete terms and the criteria for defining a case of anaphylactic reactions,
- indication of the latency period between the administration of the vaccine and the occurrence of the symptoms,
- indication which allergies and which triggers for these allergies are known in the history of the patients in concrete terms,
- indication of existing underlying diseases of the persons affected (in particular mastocytosis, mast-cell activation syndrome, increased basal tryptase values or urticaria),
- indication of concomitant medications,
- indication of examinations performed to rule-out or confirm differential diagnoses, in particular results of blood test (e.g. determination of tryptase in temporal connection with the event),

- information on the total number of vaccination doses administered, which are relevant for a frequency assessment of hypersensitivity reactions.

## Conclusion

The current data based on the cases recorded do not suffice to allow a conclusive, allergological risk assessment. In addition to the harmonised patient information and consent form<sup>1</sup> used in the vaccination centres, a structured questionnaire-assisted post-vaccination capture is planned for the reported cases from the register of spontaneous reports regarding this assessment relevant information.

### 3. Possible triggers and pathophysiology

Should the reported serious reactions actually be related to the vaccine, either the active ingredient itself (including its reaction/degradation products) or an excipient comes into question. According to the information provided by the manufacturer, the stopper of the vials of the vaccine BNT162b2 of the company Biontech/Pfizer is not made of natural rubber latex, so that traces of latex seem an improbable source to trigger an IgE-mediated allergic reaction to latex in connection with the administration of the vaccine. According to published information from the manufacturer, in addition to the active ingredient, the following excipients are contained in the vaccine:

- ALC-0315 = (4-hydroxybutyl)azandiyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate),
- ALC-0159 = 2-[(polyethyleneglycol)-2000]-N,N-ditetradecylacetamide,
- 2-distearoyl-sn-glycero-3 phosphocholine,
- Cholesterol,
- Potassium chloride,
- Potassium-dihydrogen-phosphate,
- Sodium chloride,
- Di-sodium-hydrogenphosphate-dihydrate,
- Saccharose,

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<sup>1</sup> <https://www.zusammengegencorona.de/impfen/wo-kann-man-sich-impfen-lassen/>

- Water for injections,
- An adjuvant is not contained in the vaccine, nor is a preservative, or protein from hen's eggs.

The four lipids mentioned first in the list form the lipid nanoparticles (LNP) in the BNT162b2 vaccine which include the mRNA. These are two structural lipids (2-Distearoyl-sn-glycero-3 phosphocholine, cholesterol) and two functional lipids (ALC-0315, ALC-0159). One of them (ALC-0159) is PEGylated, i.e., it contains a polyethylene glycol(PEG)-polymer with a molar weight of around 2000g/mol (PEG 2000). This is equivalent to a medium size compared with the PEG-lengths used in a number of cosmetics and medicinal products as additives or for PEGylation of medicines (of 300 to around 40,000 g/mol).

The lipid nanoparticles resemble liposomes which have already been used in pharmaceutical preparations for many years. These liposomes serve as carriers for active ingredients of medicines. Some of the liposome-/LNP-containing medicinal products also contain a PEGylated lipid (e. g. in Caelyx pegylated liposomal® or Onpattro®). The PEG-chains at the surface form a hydrate envelope around the liposome/LNP. This will increase stability and will prevent opsonisation, i. e. the mechanism by which the surface of the foreign cells (e. g. bacteria, viruses) which entered the body is covered with antibodies and factors of the complement system. This increases the stability and the half-life of the lipid particles.

Possible pseudo-allergic (non-IgE mediated) reactions (so-called CARPA, complement activation-related pseudoallergy) were described in connection with liposomes [3, 4]: They are partly considered as due to binding of pre-existing anti-PEG-IgM to the liposomes with subsequent complement activation. Clinical symptoms described caused by this non-IgE mediated hypersensitivity included dyspnoea, tachypnoea, hypotension, and hypertension shortly after intravenous administration of other liposome-containing medicinal products.

Regardless for the PEGylation, liposomes also have the potential to activate complement non-specifically (depending on their different surface structures and charge) [3].

Possible sensitisation to PEG by previous use of cosmetics or PEG-containing medicinal products is possible. Little is known about the prevalence of anti-PEG antibodies in the population. Some authors report high prevalence in certain groups [4]. Furthermore, hints pointing to a possible significance of IgE in triggering PEG-induced hypersensitivity are under discussion [5]. Allergic reactions after the use of PEG as an excipient in a number of products have been described. It is also described as a “hidden” allergen [5, 6].

## **Conclusion**

In summary, the lipid nanoparticles contained in the vaccine, and, in particular, the PEG contained in the vaccine, could be considered as agents triggering hypersensitivity reactions. From the patho-mechanical point of view, potentially pre-existing anti-PEG-IgM and/or IgG (theoretically: IgE also possible) in vaccinees could also be present (sensitisation could occur e.g. by cosmetics) [4, 7], or even be caused by the first vaccination itself. Alternatively, the hypersensitivity reaction is non-specifically (non-immunoglobulin mediated) caused as described above by lipid particles. Predictive test methods, which could point to or rule out the occurrence of a (pseudo) allergic intolerance reaction in connection with a COVID-19 vaccination, are not available.

These non-IgE mediated intolerance reactions can manifest themselves as clinically serious (anaphylactoid) symptoms, and, as a rule, occur rapidly after the administration. It is therefore recommended that personnel, accommodation, and technical facilities for emergency treatments at vaccination centres are available.

Based on the data currently available (as per 23 December 2020), the Paul-Ehrlich-Institut holds the view that a generally increased risk of serious adverse effects for persons with known atopic/allergic diseases cannot be deduced for vaccination with BNT162b2. Unlike the UK, the EU has no contraindications in place for persons with allergies or persons with anaphylactic reactions in the history. However, a previously known allergy to the substances contained in the vaccine (e. g. PEG) presents a contraindication, as well as a reaction to the first dose of the COVID-19 vaccine, which presents a contraindication for administering

the second dose. In compliance with the European SmPC<sup>2</sup>, a post-vaccination follow-up observation of at least 15 minutes should take place for all persons vaccinated. In the event of a serious allergic intolerance reaction after the administration of the vaccine, appropriate medical treatment and supervision should always be available.

## Bibliography

- [1] Medicines and Healthcare products Regulatory Agency (MHRA). Confirmation of guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination with the Pfizer/BioNTech vaccine. Press report of 9 Dec. 2020.  
<https://www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine>, (last viewed: 17 Dec. 2020)
- [2] MHRA Public Assessment Report - Authorisation for Temporary Supply COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA) concentrate for solution for injection (as per 11 Dec. 2020)  
<https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine> (last viewed: 17 Dec. 2020)
- [3] Inglut CT, Sorrin AJ, Kuruppu T, Vig S, Cicalo J, Ahmad H, Huang HC. Immunological and Toxicological Considerations for the Design of Liposomes. *Nanomaterials (Basel)*. 2020;10:190.
- [4] Mohamed M, Abu Lila AS, Shimizu T, Alaaeldin E, Hussein A, Sarhan HA, Szebeni J, Ishida T. PEGylated liposomes: immunological responses. *Sci Technol Adv Mater* 2019;20:710-724.
- [5] Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology*. 2016;46:907-922.
- [6] Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis. *Allergy, Asthma & Clinical Immunology*. 2016;12:67.

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<sup>2</sup> [https://ec.europa.eu/health/documents/community-register/2020/20201221150522/anx\\_150522\\_de.pdf](https://ec.europa.eu/health/documents/community-register/2020/20201221150522/anx_150522_de.pdf)

- [7] Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: Properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. *Adv Drug Deliv Rev.* 2020;154-155:163-175.