Note on Reference Guideline for Excipients with a known action or effect

For the Prequalification Programme of Medicines (PQT/MED), reference is made to the European Commission guideline "Excipients in the labelling and package leaflet of medicinal products for human use" and its annexes. This provides a harmonised framework for the safe and transparent communication of excipient information to patients and health care providers.

However, for the product information published as part 3 and 4 in the WHO Public Assessment Reports for products prequalified via the full assessment route some exceptions apply:

- **Lactose**: In PQT/MED, a differentiation is made between *the warning for patients with congenital lactase deficiency* and *lactose intolerance in other patients*. In addition, if the lactose used is of animal origin, the product information will also include a warning related to milk protein content.

For the SmPC (WHOPAR part 4)

4.4 Special warnings and precautions for use

1. Lactose wording concerning ***serious (congenital) genetic disorders***
(Threshold zero)
Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless absolutely necessary.

2. Lactose wording concerning ***lactose intolerance***
(Where lactose ≤ 400 mg per dose)
The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

(Where lactose > 400 mg per dose)
The small amount of lactose in each dose may cause symptoms of intolerance in other patients.

3. Lactose wording concerning ***cow's milk protein allergy***
(Threshold zero; only applicable to lactose of bovine origin)
for products given orally:
Patients who are allergic to cow's milk proteins must not be given this medicine unless absolutely necessary.
for products given parentally:
Patients who are allergic to cow's milk must not be given this medicine as it may contain trace amounts of cow's milk protein.

4. Lactose wording concerning ***diabetes***
(Threshold 5 g per dose)
Lactose is a source of glucose. Patients with concurrent diabetes should take account of the amount of lactose in this medicine (x in each <dosage unit>).

This is phrased analogously in the PIL (WHOPAR part 3).

- **Sodium**: For sodium, PQT/MED highlights in section 6 .1 of the SmPC whether a formulation can be considered *essentially sodium free*.

For the SmPC (WHOPAR part 4)
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Excipients with potential clinical effect
This heading is not included for sodium if the medicine is 'essentially sodium free'; instead a statement is included in section 6.1
6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
If a product contains an API(s) and/or excipients that are sodium salts, but the total quantity of sodium is less than 1 mmol (23 mg) per dosage unit:
This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per <dosage unit, e.g. tablet>.
This is phrased analogously in the PIL (WHOPAR part 3).

Furthermore, if any excipient warnings are included, the WHOPAR product information states:
"It is important to consider the contribution of excipients from all the medicines that the patient is taking."