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## Questions and answers on sodium used as an excipient in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [2].



# Questions and answers on sodium used as an excipient in medicinal products for human use

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## 1. What is sodium and why is it used as an excipient?

Sodium is an essential nutrient. It is the principal cation in the extracellular fluid (ECF) and has a key role in maintaining fluid balance, acid base balance, muscle and nerve activity and transport of nutrients across cell membranes. The main source of dietary sodium is sodium chloride (which the majority of people know as common table salt).

Excipients presented as sodium salts are most commonly used to increase solubility. Other sodium-containing excipients may be used for disintegration, chelation, lubrication, binding, emulsifying, stabilising, colouring or antimicrobial properties.

## 2. Which medicinal products contain sodium?

Sodium can be included in medicines in different forms. It can be used as:

- the active therapeutic moiety e.g. in sodium chloride to replace physiological sodium;
- part of the active substance e.g. when an active moiety is presented as a sodium salt, such as in sodium diclofenac;
- part of the excipient e.g. sodium bicarbonate.
- in the preparation of the medicine prior to administration e.g. dissolution in sodium chloride prior to infusion.

Sodium can be found in, for example, effervescent medicines. In such medicines, sodium-containing salts, including sodium bicarbonate and sodium carbonate, are commonly used with acidic agents such as citric or tartaric acid, to cause a reaction in water that produces carbon dioxide (CO<sub>2</sub>). The CO<sub>2</sub> leads to the resultant fizzing of the effervescent powder [13]. In other types of dosage forms, large quantities of sodium salts may be required to enhance the solubility of a medicine. Most medicines that contain high levels of sodium are therefore likely to be effervescent or soluble; however, there may be other medicines that also contain high amounts of sodium.

- 1) The sodium content of a medicine is known to the regulatory authorities and marketing authorization holders and would normally be available upon request. In some countries, the information is publicly available through NCA databases or other national provisions. An evaluation of the data reveals that the sodium content of medicines can be very high. For example the maximum daily dose of an effervescent medicine can contain 175 mmol of sodium (201% of the WHO recommended maximum daily intake for sodium for an adult).
- 2) Many medications that are high in sodium are commonly used for a wide variety of conditions and are often available over the counter (OTC) without a prescription. This reduces the opportunity for pharmacists and other health care professionals to advise people on sodium levels.
- 3) People who have a preference or need for medicines that dissolve, may be taking several medicinal products in a dissolvable form. This additive effect could have a significant impact on their sodium intake.

## 3. What are the safety concerns?

Increasing the level of sodium in the body causes an expansion of the extracellular fluid which increases blood pressure (BP) [15]. Maintaining steady sodium levels is principally achieved through

regulation of excretion through the kidneys (renal excretion) [15, 19]. The capacity for renal excretion is lower in the very young and the elderly [15].

High intake of table salt in food is associated with high BP (hypertension) and stroke in adults [15, 19].

A study in 1,292,337 patients over the age of 18 recently reported that the high sodium content of some effervescent, soluble and dispersible medicines might similarly be associated with an increased risk of cardiovascular disease [5]. Risk was measured using a statistic known as the odds ratio (OR) and presented including a confidence interval which shows the range of risks that may be true. In the study, patients who survived either a heart attack or a stroke or who died of a cardiovascular condition were 1.16 (1.12–1.21) times more likely to have been prescribed an effervescent, soluble or dispersible medicine than patients who did not suffer one of these events. The patients who survived a stroke were 1.22 (1.16–1.29) times more likely to have been prescribed a medicine that dissolves and patients with high BP (hypertension) were 7.18 (6.74–7.65) times more likely to have had prescriptions for dissolvable medicines.

The study has been criticised because it did not look separately at the risk in patients who took medicines for a long time and those who only took medicines for a very short length of time. Those patients taking medicines regularly and for a prolonged period of time might be expected to be at higher risk from sodium in medicines than those patients taking only a short-term course of treatment. Another criticism of the study is that it was not able to consider the amount of sodium patients were having in their diets as this information is not available in the database that was used for the study. There are likely to have been differences in the amounts of sodium patients were having in their diet which, independent of the salt in their medicines, may have affected their risk of cardiovascular disease. Despite the criticisms of the study, the association between hypertension and high sodium-containing effervescent, soluble and dispersible medicines was very strong (OR: 7.18), and so is likely to represent a true association.

Increasing long-term intake of dietary sodium has been shown to increase BP across all study populations and age ranges [10]. Prolonged high BP has been associated with stroke, myocardial infarction, heart failure and kidney disease and has also been linked to dementia and premature death [9]. Several large studies (meta-analyses) have reported an increased risk of stroke with increased dietary sodium [1, 11, 14, 16]. Reducing salt has been shown to significantly reduce BP [1, 3, 7, 12] and lower BP has been proven to reduce cardiovascular disease. The effect of low salt diets on BP is not always maintained beyond 6 months, but this is felt to reflect the difficulty in maintaining a low salt diet, rather than salt reduction having only a short-term effect on BP [15].

Young babies have lower capacity for removing sodium from the body. Acute high sodium intakes from any source can result in dangerously raised sodium levels in the blood (hypernatraemia). This can result most commonly in events including listlessness, serious dehydration and seizures [8].

Chronic high dietary sodium intake can raise blood pressure in children which increases the risk of hypertension and cardiovascular disease in adulthood [15, 19]. High dietary sodium intakes in childhood are also associated with the development of a preference in later life for salty food [18].

The WHO recommends that adults consume less than 5 g of sodium chloride (table salt) per day (equivalent to less than 2 g (or 87 mmol) sodium per day). Individual countries have their own guidance.

For children, the WHO advise that recommended maximum daily intakes should be proportional to adults and based on energy requirements [19].

An EU Framework on Voluntary National Salt initiatives [4] has been agreed at population level, in order to achieve the national or WHO recommendations.

## 4. What are the reasons for updating the information in the package leaflet?

It is important that patients, parents, caregivers, pharmacists, prescribers and other healthcare professionals are able to easily identify how much sodium is present in medicines, especially given that some medicines affected by this issue are available OTC with minimal chance for a healthcare professional to offer any advice on sodium and potential risks.

Information on sodium should therefore be readily available to everyone in an understandable format in the product information, to allow more informed decisions to be made about whether a medicine and its ingredients are appropriate for the patient. Such information will be particularly important for people who are on sodium restricted diets or have pre-existing cardiovascular disease and who need to take medicines on a regular basis.

The concerns with the current labelling of sodium are:

- Sodium may not be familiar to patients, parents and other caregivers as being part of sodium chloride and therefore the main component of dietary salt (common cooking salt).
- The threshold level below which a medicine is considered sodium-free is 1mmol per single dose. This is a low level of sodium – only 1.1% of the WHO recommended maximum daily intake. Any medicine with more than 1 mmol of sodium per single dose includes a warning that its use should be taken into consideration by patients on a low salt diet. No distinction is made between medicines that contain relatively low levels of sodium and those that contain exceedingly high levels of sodium (such as some effervescent products where each dose represents 25% of the WHO recommended maximum daily amount for dietary sodium). It is therefore difficult for patients and prescribers to appreciate which medicines have particularly high levels of sodium.
- Sodium is presented in units of mmol or mg and neither may be meaningful to patients or prescribers.
- The high levels of sodium in some medicines may not be appreciated by patients or healthcare professionals.

All sodium salts are soluble and therefore even sodium bound in complex molecules would be expected to dissolve and exert a physiological effect. Information for the physician and patient in the SmPC and PL should therefore relate to the total dose of sodium in the medicine irrespective of whether it derives from the active substance, the diluent (as specified in the SmPC) or the excipients.

The proposed updates to the labelling of sodium include defining 3 thresholds and presenting the sodium content in a clear and meaningful way.

The new proposals introduce an additional threshold to define levels of sodium in medicines that are considered to be 'high'. There is no evidence to suggest what level of sodium in medicines is acceptable and this will vary by individual. However, it is proposed that any product where the maximum daily dose contains  $\geq 17$  mmol (391 mg) sodium (approximately 20% of the WHO recommended maximum daily intake for sodium), should be considered as having a 'high' sodium content. This is an empirical figure but is based on the fact that the intake of sodium through medicines is in addition to dietary sodium and many people already consume too much sodium through salt in their diet.

The three proposed thresholds are  $<1$  mmol per single dose,  $\geq 1$  mmol per single dose and  $\geq 17$  mmol per maximum recommended daily dose.

Medicines containing <1 mmol sodium per dose are considered to be essentially sodium-free. If a medicine contains more than 1 mmol (23 mg) per single dose, the amount and proportion of the WHO daily recommended intake of dietary sodium that this represents will be provided in Section 2 of the PL and Section 2 of the SmPC. If a medicine may be used regularly and/or for a prolonged period (as defined below) and contains more than 17 mmol (391 mg) in the maximum daily recommended dose, the number of doses that a patient would need to take in a day to reach the 17mmol sodium threshold will be provided in the PL to enable the patient to determine if, based on their own posology, they are taking a 'high' dose of sodium through their medicine. These patients will be advised to speak to their healthcare professional, especially if they have been advised to go on a low salt diet.

As an example, if one tablet contains 250 mg (or about 11 mmol) sodium and a maximum of four tablets may be taken in a day, this corresponds to a maximum daily dose of 1 g of sodium (approximately 44 mmol). This would be the equivalent to approximately 50% of the 2 g (or 87 mmol) of sodium that the WHO recommends to be the maximum daily dietary intake for an adult. With the new proposal, a patient or healthcare professional will be able to clearly see how much sodium they are ingesting in a single dose, that the maximum daily dose of the medicine provides half of their maximum daily recommended intake of sodium and that taking more than one tablet per day takes them above the threshold for medicines.

The criteria for products considered to be 'high' dose and to warrant a warning are:

- $\geq 17$ mmol sodium in the maximum daily dose, and
- for long term use or regular exposure.

As a general guide 'long-term use' is considered to be continuous daily use for > 1 month and 'regular use' is considered to be repeated use for more than 2 days every week.

The 'high' dose threshold will not apply to medicines that are indicated for short-term use only.

For parenteral products the amount of sodium should be expressed in mg per unit dose or mg per ml solution as appropriate. For parenterals with variable (e.g. weight-based) dosing sodium content may be expressed in mg per vial.

These updates to the excipient guideline do not replace any warnings or contraindications relating to sodium that already exist in product information that are not obviously superseded by the new proposals (e.g. the risk of hypernatraemia in paediatric medicines should be retained).

#### **Worked examples for each of the proposed thresholds:**

##### <1mmol per dose

This medicine contains less than 1 mmol sodium (23 mg) per <dosage unit/volume>, i.e. is essentially 'sodium-free'

##### $\geq 1$ mmol per single dose

This medicine contains 100 mg sodium (main component of cooking salt) in each tablet. This is equivalent to 5% of the recommended maximum daily dietary intake of sodium for an adult.

##### $\geq 17$ mmol per maximum recommended daily dose

This medicine contains 100 mg sodium (main component of cooking salt) in each tablet. This is equivalent to 5% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor or pharmacist if you need 4 or more tablets daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

## 5. Updated information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
<b>Sodium</b>	Oral, parenteral	Less than 1 mmol (23 mg) per dose	This medicine contains less than 1 mmol sodium (23 mg) per <dosage unit><unit volume>, that is to say essentially 'sodium-free'.	<p>1 mmol of sodium (Na) = 23 mg Na = 58.4 mg salt (NaCl).</p> <p>Information relates to a threshold based on the total amount of sodium in the medicinal product.</p> <p>It is especially relevant to products used in children or in patients on a low sodium diet, to provide information to prescribers and reassurance to parents or patients concerning the low level of sodium in the product.</p>
		1 mmol (23 mg) per dose	This medicine contains x mg sodium (main component of cooking/table salt) in each <dosage unit><unit volume>. This is equivalent to y% of the recommended maximum daily dietary intake of sodium for an adult.	<p>For parenterals with variable (e.g. weight-based) dosing sodium content may be expressed in mg per vial.</p> <p>Proposed wording for SmPC:</p> <p>"This medicinal product contains x mg sodium per &lt;dosage unit&gt;, equivalent to y% of the WHO recommended maximum daily intake of 2 g sodium for an adult."</p>

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
		17 mmol (391 mg) in the maximum daily dose	Talk to your doctor or pharmacist if you need <Z> or more <dosage units> daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.	<p>This applies only to products for which the labelled posology allows the product to be taken on a daily basis for &gt; 1 month or repeated use for more than 2 days every week.</p> <p>17 mmol (391 mg) is approximately 20% of the WHO adult recommended maximum daily dietary intake of 2 g sodium and is considered to represent 'high' sodium.</p> <p>This is also relevant for children, where the maximum daily intake is considered to be proportional to adults and based on energy requirements.</p> <p>&lt;Z doses&gt; reflects the lowest number of dosage units for which the threshold of 17 mmol (391 mg) of sodium is reached/ exceeded. Round down to the nearest whole number.</p> <p>For SmPC wording please refer to PRAC recommendation: "<i>1.3. Sodium-containing effervescent, dispersible and soluble medicines – Cardiovascular events</i>" (<a href="https://www.ema.europa.eu/en/PRAC/234960/2015">EMA/PRAC/234960/2015</a>).</p>



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## Annex 1 - Information in the package leaflet as per 2003 Guideline [6]

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sodium	Parenteral	Less than 1 mmol per <dose>	This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. essentially 'sodium- free'.	Information relates to a threshold based on the total amount of Na <sup>+</sup> in the medicinal product. It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of Na <sup>+</sup> in the product.
	Oral Parenteral	1 mmol per <dose>	This medicinal product contains x mmol (or y mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet	