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Questions and answers on sodium in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev.1)

Draft

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Questions and answers on sodium in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1)

1. Background

Following the European Commission decision to revise the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) [1], a multidisciplinary group of experts involving SWP (lead), QWP, PDCO, PRAC (ex PVWP), CMD(h), VWP, BWP and BPWP was created in 2011.

The objective of this group is to update the labelling of selected excipients listed in the Annex of the above mentioned EC guideline, as well as to add new excipients to the list, based on a review of their safety. The main safety aspects to be addressed were summarised in a concept paper published in March 2012 [2].

Draft questions and answers (Q&A) documents on excipients are progressively released for public consultation. They include proposals for new or updated information for the label and package leaflet.

When one or several Q&As have been finalised, the new information in the package leaflet will be included in a revised annex of the guideline.

For more information see the Excipients labelling webpage on the EMA website.

2. 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).

Sodium is used in medicines both as the main ingredient (for example where medicines are intended to replace physiological sodium, or the active pharmaceutical ingredient is a sodium salt), and also as an excipient. The former is out of scope of this Q&A.

Sodium salts used as excipients are most commonly used to increase solubility, but they can also be used for disintegration, chelation, lubrication, binding, emulsifying and stabilising. They may be also added for colouring or for antimicrobial properties.

3. Which medicinal products contain sodium?

Sodium can be found in effervescent medicines. In those 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_2). The CO_2 leads to the resultant fizzing of the effervescent powder [3]. 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. All sodium salts are soluble and therefore even sodium bound in complex molecules would be expected to dissolve and exert a physiological effect.

UK medicines information (UKMI) has prepared a list of the sodium content of a variety of medicinal products available in the UK [4]. The list is not exhaustive and includes products containing a sodium salt as an excipient or as an active ingredient. The list is useful for illustrating that the sodium content of medicines is variable and also raises the following issues.

1) 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.

4. What are the safety concerns?

Increasing the level of sodium in the body causes an expansion of ECF which increases blood pressure (BP) [5]. Maintaining steady sodium levels is principally achieved through regulation of excretion through the kidneys (renal excretion) [5, 6]. The capacity for renal excretion is lower in the very young and the elderly [5].

High intake of table salt is associated with high BP (hypertension) and stroke in adults [5, 6].

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 be associated with an increased risk of cardiovascular disease [7]. Risk was measured using a statistic known as the odds ratio 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. All of these results were statistically significant indicating that there is likely to be a true association between the high sodium content of effervescent, dispersible and soluble medicines and cardiovascular disease.

The study has been criticised because it did not look separately at 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, and so is likely to represent a true association. This is supported by the fact that an association is already accepted to exist between high dietary sodium and cardiovascular events, especially hypertension.

Increasing long-term intake of dietary sodium has been shown to increase BP across all study populations and age ranges [8]. 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 [10–13]. Reducing salt has been shown to significantly reduce BP [12, 14–16] 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 [5].

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 [17].

Chronic high dietary sodium intake can raise blood pressure in children which increases the risk of hypertension and cardiovascular disease in adulthood [5, 6]. High dietary sodium intakes in childhood are also associated with the development of a preference in later life for salty food [18].

The WHO recommend adults to consume less than 5g of sodium chloride (table salt) per day (equivalent to less than 2g (or 87 mmol) sodium per day). Individual countries have their own guidance; for example in the UK it is recommended for adults to have less than 6g of sodium chloride per day (equivalent to less than 2.4g (or 104mmol) sodium per day).

For children, the WHO advise that recommended maximum daily intakes should be proportional to adults and based on energy requirements [6]. An EU Framework on Voluntary National Salt initiatives [19] has been agreed at population level, in order to achieve the national or WHO recommendations.

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

It is important that patients, parents, carers, pharmacists, prescribers and other healthcare professionals are able to easily identify how much sodium is present in medicines, especially given that many 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 be readily available to everyone in an understandable format in the product information and will allow more informed decisions to be made about whether a medicine and its ingredients are appropriate for the patient. This information will be particularly important for people who are on sodium restricted diets or have pre-existing cardiovascular disease and especially those who need to take medicines on a regular basis.

The concerns with the current labelling of sodium as an excipient are:

- Sodium may not be familiar to patients and parents as being part of sodium chloride and the main component of dietary salt (common table salt).
- The threshold level below which a medicine is considered sodium-free is 1mmol / dose. This is a low level of sodium and only 1.1% of the WHO recommended maximum daily intake. Any

medicine with more than 1 mmol of sodium per 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 (e.g. approx. 22 mmol / dose for some effervescent products meaning each dose represents 25% of the WHO recommended maximum daily amount for 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.

The proposed updates to the labelling of sodium therefore include defining and presenting sodium content in a clear and meaningful way. Thus the sodium content in the maximum daily dose recommended for a medicine will be presented as a proportion of the WHO maximum recommended daily dietary intake for sodium. So for example, if one tablet contains 250mg (or about 11mmol) sodium and a maximum of four tablets may be taken in a day, this corresponds to a maximum daily dose of 1g of sodium (approximately 44mmol). This would be the equivalent to approximately 50% of the 2g (or 87mmol) of sodium that the WHO recommends to be the maximum daily dietary intake for an adult. A patient or healthcare professional will be able to clearly see that the maximum daily dose of the medicine provides half of their maximum daily recommended intake of sodium.

The proposal also introduces an additional threshold to define levels of sodium in medicines 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 ≥ 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 are already consuming too much sodium through common salt in their diet.

162 ***Information in the package leaflet as per the 2003 Guideline***

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+ 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+ 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	

5. Proposal for an updated information in the package leaflet

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. it is essentially 'sodium- free'.	1 mmol of sodium (Na) = 23 mg Na = 57 mg table salt (NaCl).
	Oral Parenteral	1 mmol (23 mg) per dose	One dose of this medicinal product contains <X mg> sodium (found in table salt). This is equivalent to <Y%> of the recommended maximum daily intake of sodium for an adult.	
	Oral Parenteral	17 mmol (391 mg) in the maximum daily dose	The maximum recommended daily dose of this medicinal product contains <X mg> sodium (found in table salt). This is equivalent to <Y%> of the recommended maximum daily intake of sodium for an adult. Talk to your pharmacist or doctor if <you> <or> <your child> need(s) [product name] on a daily basis for a prolonged period of time, especially if <you><they> have been advised to follow a low salt diet.	17mmol (391mg) is approximately 20% of the WHO adult recommended maximum daily dietary intake for sodium and is considered to represent 'high' sodium. This is also relevant for children, where the maximum daily intake is considered to be proportional to adults and based on energy requirements.

***** Note: The threshold is a value, equal to or above which it is necessary to provide the information stated [1].

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