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

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Comments should be provided using this [template](#). The completed comments form should be sent to excipients@ema.europa.eu

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

18 **1. Background**

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

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

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

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

31 For more information see the [Excipients labelling webpage](#) on the EMA website.

32 **2. What is sodium and why is it used as an excipient?**

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

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

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

43 **3. Which medicinal products contain sodium?**

44 Sodium can be found in effervescent medicines. In those medicines, sodium-containing salts, including
45 sodium bicarbonate and sodium carbonate, are commonly used with acidic agents such as citric or
46 tartaric acid, to cause a reaction in water that produces carbon dioxide (CO₂). The CO₂ leads to the
47 resultant fizzing of the effervescent powder [3]. Large quantities of sodium salts may be required to
48 enhance the solubility of a medicine. Most medicines that contain high levels of sodium are therefore

49 likely to be effervescent or soluble, however, there may be other medicines that also contain high
50 amounts of sodium. All sodium salts are soluble and therefore even sodium bound in complex
51 molecules would be expected to dissolve and exert a physiological effect.

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

56 1) The sodium content of medicines can be very high. For example the maximum daily dose of an
57 effervescent medicine can contain 175 mmol of sodium (201% of the WHO recommended
58 maximum daily intake for sodium for an adult).

59 2) Many medications that are high in sodium are commonly used for a wide variety of conditions
60 and are often available over the counter (OTC) without a prescription. This reduces the
61 opportunity for pharmacists and other health care professionals to advise people on sodium
62 levels.

63 3) People who have a preference or need for medicines that dissolve, may be taking several
64 medicinal products in a dissolvable form. This additive effect could have a significant impact on
65 their sodium intake.

66 **4. What are the safety concerns?**

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

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

72 A study in 1,292,337 patients over the age of 18 recently reported that the high sodium content of
73 some effervescent, soluble and dispersible medicines might be associated with an increased risk of
74 cardiovascular disease [7]. Risk was measured using a statistic known as the odds ratio and presented
75 including a confidence interval which shows the range of risks that may be true. In the study, patients
76 who survived either a heart attack or a stroke or who died of a cardiovascular condition were 1.16
77 (1.12–1.21) times more likely to have been prescribed an effervescent, soluble or dispersible medicine
78 than patients who did not suffer one of these events. The patients who survived a stroke were 1.22
79 (1.16–1.29) times more likely to have been prescribed a medicine that dissolves and patients with high
80 BP (hypertension) were 7.18 (6.74–7.65) times more likely to have had prescriptions for dissolvable
81 medicines. All of these results were statistically significant indicating that there is likely to be a true
82 association between the high sodium content of effervescent, dispersible and soluble medicines and
83 cardiovascular disease.

84 The study has been criticised because it did not look separately at patients who took medicines for a
85 long time and those who only took medicines for a very short length of time. Those patients taking
86 medicines regularly and for a prolonged period of time might be expected to be at higher risk from
87 sodium in medicines than those patients taking only a short-term course of treatment. Another
88 criticism of the study is that it was not able to consider the amount of sodium patients were having in
89 their diets as this information is not available in the database that was used for the study. There are
90 likely to have been differences in the amounts of sodium patients were having in their diet which,
91 independent of the salt in their medicines, may have affected their risk of cardiovascular disease.

92 Despite the criticisms of the study, the association between hypertension and high sodium-containing
93 effervescent, soluble and dispersible medicines was very strong, and so is likely to represent a true
94 association. This is supported by the fact that an association is already accepted to exist between high
95 dietary sodium and cardiovascular events, especially hypertension.

96 Increasing long-term intake of dietary sodium has been shown to increase BP across all study
97 populations and age ranges [8]. Prolonged high BP has been associated with stroke, myocardial
98 infarction, heart failure and kidney disease and has also been linked to dementia and premature
99 death [9]. Several large studies (meta-analyses) have reported an increased risk of stroke with
100 increased dietary sodium [10–13]. Reducing salt has been shown to significantly reduce BP [12, 14–
101 16] and lower BP has been proven to reduce cardiovascular disease. The effect of low salt diets on BP
102 is not always maintained beyond 6 months, but this is felt to reflect the difficulty in maintaining a low
103 salt diet, rather than salt reduction having only a short-term effect on BP [5].

104 Young babies have lower capacity for removing sodium from the body. Acute high sodium intakes from
105 any source can result in dangerously raised sodium levels in the blood (hypernatraemia). This can
106 result most commonly in events including listlessness, serious dehydration and seizures [17].

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

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

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

118 **5. What are the reasons for updating the information in the** 119 **package leaflet?**

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

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

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

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

134 medicine with more than 1 mmol of sodium per dose includes a warning that its use should be
135 taken into consideration by patients on a low salt diet. No distinction is made between medicines
136 that contain relatively low levels of sodium and those that contain exceedingly high levels of
137 sodium (e.g. approx. 22 mmol / dose for some effervescent products meaning each dose
138 represents 25% of the WHO recommended maximum daily amount for sodium). It is therefore
139 difficult for patients and prescribers to appreciate which medicines have particularly high levels of
140 sodium.

- 141 • Sodium is presented in units of mmol or mg and neither may be meaningful to patients or
142 prescribers.

143 The high levels of sodium in some medicines may not be appreciated by patients or healthcare
144 professionals.

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

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

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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	

163 **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.

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

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