10 October 2017
EMA/CHMP/623211/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft questions and answers on sodium' (EMA/CHMP/338679/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Verla-Pharm Arzneimittel, Hauptstraße 98, 82327 Tutzing, Germany
2	The European Consumer Organisation (BEUC)
3	Bundesverband der Pharmazeutischen Industrie – BPI e. V. - German Pharmaceutical Industry Association
4	Reckitt Benckiser Healthcare (UK) Limited
5	Mylan EPD - Mylan Healthcare GmbH - RA Department
6	Sandoz
7	Teva Pharmaceuticals Ltd
8	AESGP
9	EFPIA – Pär Tellner
10	Weleda AG, Schwäbisch Gmünd (Germany)
11	International Plasma Fractionation Association (IPFA)
12	PAINT-Consult - Dr. Jörg Fuchs
13	Medicines Evaluation Board - The Netherlands

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
3	Sodium salts are used in many parenteral medicinal products for isotonization or as a buffer. The German Homoeopathic Pharmacopoeia even states in Method 11, Parenteral preparations / Liquid dilutions for injection: "*Sodium chloride is normally used as the isotonising agent"*. Further it is required that "*any isotonising agents other than sodium chloride must be declared*". The quantity of sodium in these kinds of products is very low. A 0.9 % sodium chloride solution is isotonic. For an ampoule with 1 ml solution this corresponds to a content of 3.54 mg or 0.154 mMol sodium. As normally the frequency of administration lies between one time per week and one time per day the maximum daily dose does not exceed 3.54 mg sodium (corresponding to 0.177 % of the recommended maximum dose of 2 g sodium/day). Therefore, it seems to be acceptable to classify these products as essentially 'sodium-free'. In the rare cases of acute diseases where the products have to be given several times per day this treatment takes place only over a short time, so the effect will be also negligible. In the „Besonderheitenliste des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) / Version 1-11, März 2015 auf Basis der Excipients-Guideline (CPMP/463/00 Final, Juli 2003), der Arzneimittel-Warnhinweisverordnung sowie umgesetzter nationaler Stufenplanmaßnahmen" this circumstance is taken into account. Under the passus „Sodium compounds in parenterals" it is stated: "*At pH adjustments and isotonization in small quantities [content not over 0.154 mmol (or 3.54 mg) Na^+ per ml solution of single dose] the Note for sodium compounds can be omitted*" (see also our first specific comments).	The Excipient Guideline with respect to parenteral products containing <1mmol sodium per <dose> has not changed materially and so should be applied as before.

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7	We would like to have clarity regarding the implementation: In case that the medicine contains more than 1 mmol per dose **and** more than 17 mmol in the maximum daily dose, it is unclear if we need to use the wording for the threshold *1 mmol (23 mg) per dose* **in addition** to the wording for the threshold *17 mmol (391 mg) in the maximum daily dose*.	If a single dose contains >1mmol AND the max daily dose contains >17mmol **the wording for both thresholds would need to be applied.** This is more informative for the patient/HCP as it provides them with information they need if they take less than the max daily dose. The Q&A has been updated to make this clear.
8	Article 63(2) of Directive 2001/83/EC as well as the Guideline On The Readability Of The Labelling And Package Leaflet Of Medicinal Products For Human Use requires…*that the package leaflet must be written to be clear and understandable, enabling the users to act appropriately*. Therefore, the proposed labelling changes should be restricted to those medications, where the knowledge of the sodium content relative to the WHO recommendation could be of any use for a patient and she/he gets appropriate advice as to what should be done in her/his particular situation.	The current wording in the Excipient Guideline already applies to both oral and parenteral products.
	Therefore, it is proposed not to change the labelling for parenteral drugs, as parenteral drugs are administered by Healthcare Professionals (HCPs) or administered following close advice from HCPs. The level of 17 mmol sodium will only be reached by infusions with a relatively large volume. In all these cases, sodium content is well considered by the HCPs; additional information beyond the current labelling will not provide any useful information to patients and could confuse the patient.	Not accepted. We agree that few, if any, parenteral products used regularly or long-term would deliver more than 17mmol sodium per daily and in such situations most would be administered by a HCP and the patient would be monitored. However, as self-administration of medicines is becoming more common it is possible that some parenteral products already exist, or may exist in the future, that are regularly self-administered and contain high levels of sodium. Since the current Excipient Guideline contains a warning for patients about the sodium content of all parenteral products that contain more than 1mmol per <dose> (including a warning for those on a high

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		salt diet) we consider that it is appropriate to take a more risk proportionate approach and apply the proposed warning only to products containing more than 17mmol per max daily <dose>.
	For oral preparations it should be clarified, that the additional warning for medicinal products containing >17 mmol of sodium only has to be added if the drug is intended for regular/long term use and the definition of this term (as given in the running text of the Q&A paper) should be added in the table. Medicines which have a clear restriction of duration of use in the label should be exempted in general.	Accepted. The Q&A has been updated to include definitions of long-term and regular use (consistent with the PRAC recommendation).
	For products containing between 1 and 17 mmol, the patient will receive the information: *"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"* even if the product is taken for a short period of time. The consequence to be taken by the patient is unclear as no further advice is given. What should an otherwise healthy patient do if she/ he takes such a product for a short period of time (e.g. during a common cold)? The wording of the 2003 Guideline provided more information: *"To be taken into consideration by patients on a controlled sodium diet."* To meet the requirements of Article 63(2) of Directive 2001/83/EC it should be clarified that only regular/ long term use has to be considered and the former wording of the 2003 Guideline should be maintained for the package leaflet.	Not accepted. One of the reasons for introducing an additional threshold was that patients taking medicines with low levels of sodium (~1% of the WHO allowance) were being unnecessarily advised to take the sodium content into consideration if they were on a low salt diet. It is unlikely that an otherwise healthy patient would need to take any action if she/ he takes a product that delivers between 1% and 20% of their daily recommended sodium in the max daily dose for a short period of time.

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8	Sodium salts are used in many parenteral medicinal products for isotonisation or as a buffer. The German Homoeopathic Pharmacopoeia e.g. states in "Method 11: parenteral preparations / Liquid dilutions for injection": *Sodium chloride is normally used as the isotonising agent*. The quantity of sodium in these kinds of products is very low and does not exceed 3.54 mg/ml. Therefore, they all belong to the group "Less than 1 mmol per dose" and are practically 'sodium-free'. But with a maximum of 0.154 mmol Na+ per ml solution they do not exceed the physiological value.	No response required (see also response to comment 3).
8	Since several pharmaceutical forms e.g. ampoules and eye drops can contain sodium because of the isotonisation or pH adjustment we would like to suggest an exemption for the obligation to inform patients with a specific additional phrase in the package leaflet. It should be sufficient to name the excipient which contains sodium without any other text.	The response depends on whether topical and ophthalmic preparations are considered to fall within the umbrella of 'parenterals'. If they do, parenterally-administered products containing <1mmol per dose the message provided in the PL will still be labelled as essentially sodium-free. If the sodium content of any such products exceeds the 1mmol threshold the same text as for oral products would apply. If they do not fall within the umbrella of 'parenterals', this comment is outside the scope of this review.
9	It would be very helpful for users of the guidance to have **all** recommendations on product information text associated with sodium content to be stated in this Q&A document. Currently this Q&A relates to just Package Leaflet text (see Lines 118-119) whereas EMA/PRAC/234960/2015 makes recommendations for the SmPC and label also (p.7 Recommendation, from line 38). The Excipient Guideline also has 'proposed SPC' text stated in the 'Comments' column for certain excipients e.g. Glucose. See comment for line 163.	Agreed. As the comment suggests, the Excipient Guideline already contains examples whereby accompanying text for the SmPC is included in the comments column (eg the sugars). Although the PRAC recommendation provides SmPC text for the >17mmol threshold products no SmPC text has been proposed for products containing <17mmol sodium. If no SmPC proposal is included in the Excipient Guideline there would be discordance between the SmPC and PL for the

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		majority of medicines ie those with sodium ≥1mmol per <dose> and <17mmol per <maximum daily dose>would have information on sodium in the PL but not the SmPC. Since HCPs make decisions on the most appropriate medicines for a patient and may be asked to recommend a low sodium alternative we consider it is essential that they are provided with the same information as patients. The Q&A has been updated.
9	It would be more relevant to physicians and patients if they were informed of the medicines' total maximum daily dose of sodium (including main ingredient, excipient and diluent e.g. for infusions with sodium chloride solution), and not only excipient content; according to approved dosage recommendations and methods of administration in the SmPC, rather than having to do a calculation. Especially in an emergency situation. The need for immediately understandable information was highlighted in EMA/PRAC/234960/2015 (p.7 Recommendation, line 6). See comment for lines 156-157&163.	Accepted. The sodium threshold in the existing Excipient guide currently relates to total sodium (comment column states: "Information relates to a threshold based on the total amount of Na+ in the medicinal product"). Furthermore the thresholds for the updated Guide were calculated based on total sodium dose. The PRAC recommendation provides SmPC and PL wording for products that contain sodium levels >17mmol in the maximum daily dose (irrespective of whether it derives from the active, diluent or excipient). It would therefore result in confusion (and also be irrelevant to patients) for the wording proposed in this update to relate only to sodium from excipients. The Q&A has been updated to make it clear that the sodium thresholds relate to total sodium and not just that deriving from the excipients – in line with the current guideline.
9	For parenteral products which very often have body weight based dosing	Accepted.

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	it is not always possible to estimate the amount of sodium per dose as it varies according to patient. It is difficult to define a common dose for products, which are administered via the parenteral routes and for medicinal products dosed according to the effect (for instance the insulin products, which are dosed according the biomarkers, e.g. blood glucose). Should "dose " be "<dose>" as is currently in the 2003 guideline so that in the above instance the amount of sodium per vial can be quoted instead? (See specific comments on line 163) Alternatively, it might be possible to rephrase the label text in the package leaflet to reflect the actual use, but labelling per vial is perhaps the more straightforward solution.	Where the dose of a parenteral product received by each patient may differ it is recommended to specify the total amount of sodium per vial.
9	Article 63(2) of Directive 2001/83/EC as well as the Guideline On The Readability Of The Labelling And Package Leaflet Of Medicinal Products For Human Use requires…*that the package leaflet must be written to be clear and understandable, enabling the users to act appropriately*. Therefore, the proposed labelling changes should be restricted to those medications, where the knowledge of the sodium content relative to the WHO recommendation could be of any use for a patient and she/he gets appropriate advice what should be done in her/his particular situation.	
	Parenteral drugs are administered by Healthcare Professionals (HCPs) or administered following close advice from HCPs. The level of 17 mmol sodium will only be reached by infusions with a relatively large volume. In all these cases, sodium content is well considered by the HCPs; additional information beyond the current labelling may not provide any useful information to patients and could confuse the patient.	Not accepted. See response to same comment by 8 above.

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	For oral preparations it should be clarified, that the additional warning for medicinal products containing >17 mmol of sodium only has to be added, if the drug is intended for regular/long term use and the definition of this terms (as given in the running text of the Q&A paper) should be added in the table.	Accepted. See response to same comment by 8 above.
	Drugs which have a clear restriction of duration of use in the label should be exempted in general, consequently also OTC analgesics, as they are restricted to short term use and not intended to treat chronic conditions.	Accepted. See response to same comment by 8 above.
	For products containing > 1 mmol < 17 mmol the patient will receive the information: *"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"* even if the product is taken for a short period of time. The consequence to be taken by the patient is unclear as no further advice is given. What should an otherwise healthy patient do if she/ he takes such a product for a short period of time (e.g. during a common cold)? The wording of the 2003 Guideline provided more information: *"To be taken into consideration by patients on a controlled sodium diet."* To meet the requirements of Article 63(2) of Directive 2001/83/EC it should be clarified that only regular/ long term use has to be considered and the former wording of the 2003 Guideline should be maintained for the package leaflet.	Not accepted. See response to same comment by 8 above.
9	A concern relates to the lack of a definitive value for the paediatric population. Where a medicine is developed for exclusive use in children, the proposed information on the label is not particularly helpful to the	Not accepted. The cardiovascular risk from sodium exposure in children is not as clearly defined as in adults. In children the maximum

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	parent/carer and may lead to more rather than less confusion.	recommended daily sodium intake is proportional to adults and based on energy requirements. As a result, because of the substantial difference between children of the same age in their energy requirement (and thus salt tolerance) – due to differences in their size/weight, levels of activity etc, it was considered not possible to provide more defined thresholds for children. While the proposed thresholds are based on the adult WHO salt intake, the threshold of 17mmol per day is in any case empirical. For children, the greatest risk with sodium comes from acute exposure to high doses in newborns. Medicines with relevant paediatric indications and high sodium content already include warnings about the risk of hypernatraemia, especially in those with renal impairment. The Q&A makes it clear that any such pre-existing warnings should be retained.
10	Sodium salts are used in many parenteral medicinal products for isotonization or as a buffer. The German Homoeopathic Pharmacopoeia even states in Method 11, Parenteral preparations / Liquid dilutions for injection: "*Sodium chloride is normally used as the isotonising agent"*. Further it is required that "*any isotonising agents other than sodium chloride must be declared*". The quantity of sodium in these kinds of products is very low. A 0.9 % sodium chloride solution is isotonic. For an ampoule with 1 ml solution this corresponds to a content of 3.54 mg or 0.154 mMol sodium. As normally the frequency of administration lies between one time per week and one time per day the maximum daily dose does not exceed 3.54 mg sodium (corresponding to 0.177 % of the recommended maximum dose of 2 g sodium/day). Therefore, it seems to be acceptable to classify these	Not accepted (see response to same comment by 3 above).

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	products as essentially 'sodium-free'. In the rare cases of acute diseases where the products have to be given several times per day this treatment takes place only over a short time, so the effect will be also negligible. In the „Besonderheitenliste des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) / Version 1-11, März 2015 auf Basis der Excipients-Guideline (CPMP/463/00 Final, Juli 2003), der Arzneimittel-Warnhinweisverordnung sowie umgesetzter nationaler Stufenplanmaßnahmen" this circumstance is taken into account. Under the passus „Sodium compounds in parenterals" it is stated: "*At pH adjustments and isotonization in small quantities [content not over 0.154 mmol (or 3.54 mg) Na^+ per ml solution of single dose] the Note for sodium compounds can be omitted*" (see also our first specific comments).	
11	IPFA acknowledges and supports the concern regarding the sodium content of medicines and presenting it in a meaningful way. We further appreciate the efforts of the EMA excipients drafting group to address the issue. As manufacturers of plasma derived medicinal products, sodium is found in these parenteral medicines in varying quantities due to its source, use as an excipient during the manufacturing process, or as a diluent required in the reconstitution of lyophilised products. There are constraints with respect to expressing the content in the package leaflet as proposed (per dose/ maximum daily dose), especially for some products such as human albumin solution and intravenous immunoglobulins. The dose of human albumin solution is dependent on various patient and clinical factors which results in variable dosing and no predefined maximum single dose. Therefore establishing the sodium content per	The Q&A document recommends expressing sodium per vial for variable-dosing parenterals. However, SmPCs are outside the scope of this procedure.

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	dose/maximal daily dose is not feasible. The Guideline on the Core SPC for human albumin solution (CPMP/PHVWP/BPWG/2231/99 rev.2) and Draft EMA/CHMP/BPWP/494462/2011 rev.3 does require under 6.1 List of excipients that "the content of sodium expressed in millimoles per litre]". There should be clarification on whether the individual requirements or stipulations of these Core SmPC's will take precedence. With respect to human normal immunoglobulin for intravenous administration (IVIG), the dose and dosing regimen is also dependent on the indication for use as well as expressed on a g/kg basis. A maximal single dose in 4.2 of the SmPC is set for one indication on a g/kg basis as well. Defining sodium content as proposed would therefore also not be reasonable. An alternative method of expressing sodium content for e.g. as per gram of immunoglobulin (Ig) may be more appropriate. There is no specific statement regarding sodium content in the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) EMA/CHMP/BPWP/94038/2007 rev. 3. The proposed labelling and package leaflet requirements will therefore need to accommodate the limitations with respect to dosing for these unique medicinal products. Expressing the quantity of sodium as a function of volume/mass of product would enable the healthcare provider to determine the total sodium exposure to the patient in terms of total dose received per day. It would therefore be more appropriate to have an expression of sodium in mg of sodium/mL and/or mmol of sodium/mL. Two examples of wordings already addressing those two points are provided below for two products registered via the centralised	

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	procedure: <table><tr><th>PIL</th><th>Nuwiq http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002813/WC500179340.pdf</th><th>Novoeight http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002719/WC500157553.pdf</th></tr><tr><td>2. What you need to know before you use Nuwiq/ Novoeight</td><td>Nuwiq contains sodium This medicine contains less than 1 mmol sodium (23 mg) per vial. However depending on your body weight and your dose of Nuwiq, you could receive more than one vial. This should be taken into consideration if you are on a controlled sodium diet.</td><td>NovoEight contains sodium This medicine contains 28 mg sodium (7 mg/ml) after it has been reconstituted. Talk to your doctor if you are on a controlled sodium diet.</td></tr></table>	
	• WHO recommendation for children is not clearly defined (Extract from WHO guideline: "WHO recommends a reduction in sodium intake to control blood pressure in children (strong recommendation). The recommended maximum level of intake of 2 g/day sodium in adults should be adjusted downward based on the energy requirements of children relative to those of adults"). A statement concerning sodium intake in children should be foreseen in the guideline on excipients for pharmaceutical forms which can be administered in adults and in children or in children only.	Not accepted. See response to similar comment by 9.
	• A statement concerning sodium intake for parenteral products (containing sodium or not) which can or should be diluted with a sodium chloride 9 mg/ml solution (often proposed as solution for dilution along with glucose 5% solution) not provided with the product should also be foreseen in order to alert patients about the sodium content of sodium chloride solution used for dilution.	Accepted. Product information should refer to the total sodium content including that of any diluents that are specified in the SmPC, even if it is not provided with the product.
	• Section 2 and 4.4 of the SmPC should be kept consistent with information on excipients found in the PIL. QRD Templates/Guideline on SmPC/guideline on excipients should also perhaps be updated	Partly accepted. We accept that it is important to reflect sodium appropriately

<table>
<tr><th>Stakeholder no.</th><th>General comment (if any)</th><th>Outcome (if applicable)</th></tr>
<tr><td></td><td>accordingly in order to advise on best way to word information on excipients in section 2 and 4.4 of the SmPC, especially for parenteral products.

Examples of wordings for two parenteral solutions are provided in table below (still for Nuwiq and Novoeight products):

<table>
<tr><th>SmPC</th><th>Nuwiq</th><th>Novoeight</th></tr>
<tr><td>2. QUALITATIVE AND QUANTITATIVE COMPOSITION</td><td>Excipient(s) with known effect: 7.35 mg sodium per ml reconstituted solution (18.4 mg sodium per vial).</td><td>Excipient with known effect: 0.31 mmol sodium (7 mg) per ml of reconstituted solution.</td></tr>
<tr><td>4.4 Special warnings and precautions for use</td><td>Excipient related considerations (sodium content)
This medicinal product contains less than 1 mmol sodium (23 mg) per vial.
However depending on the body weight and posology, the patient could receive more than one vial. This should be taken into consideration by patients on a controlled sodium diet.</td><td>Excipient related considerations
After reconstitution this medicinal product contains 0.31 mmol sodium (7 mg) per ml of reconstituted solution. To be taken into consideration by patients on a controlled sodium diet.</td></tr>
</table></td><td>in the SmPC. Proposals for Section 2 and Section 4.4 of the SmPC have been added to the Q&A.

The QRD Templates/Guideline on SmPC/guideline on excipients are outside the scope of this update to sodium labelling.</td></tr>
<tr><td>12</td><td>We agree with the statement provided in line 124 “Information on sodium should be ...in an understandable format...”. We at PAINT-Consult are a provider of readability tests of package leaflets and a researcher of this important patient information, with several published studies involving more than 10000 participants. See http://www.paint-consult.com/en/publikationen/publikationen/.

Our research and readability test experience informs us that texts used in package inserts must be short, precise and without difficult terms. The suggestions provided in “2. Specific comments on text” consider the findings of our extensive practical knowledge in package leaflets.</td><td>No comment required.</td></tr>
</table>

Stakeholder no.	General comment (if any)	Outcome (if applicable)
12	We agree with the statement provided in lines 130 and 131 that "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)." However, we disagree with the intention to provide the information that sodium is contained in table salt, in the excipients labelling. The package leaflet is intended to inform of the medicine and must remain focussed on this task. It is not a medium for providing general information or anything else, which is not directly related to the medicine. Extending the content of the package leaflet to include the latter would precipitate an extreme increase in the volume of text - with all of the attendant negative outcomes of same, such as overtaxing patients.	Not accepted. This proposal relates to total, rather than excipient only, sodium content. We consider it more helpful to provide the patient with the information they may need to make informed decisions on their medicine. When providing information on sodium to a lay audience, it is important to explain what sodium is, by using a common reference.
	Furthermore, most sodium-containing medicines do not contain sodium chloride. Including the proposed wording "(found in table salt)" will only mislead patients to believe that table salt is contained in the medicine.	Partly accepted. The updated Q&A refers to cooking salt rather than table salt. We do not agree that patients will think their medicine contains cooking salt and the statement, "sodium (contained in cooking salt)" is factually correct. However, it has been updated to "sodium (main component of cooking salt)".

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
n/a	8	**Comment:** We suggest to exempt products containing sodium just for pH adjustment and isotonisation completely from the obligation to inform patients in the package leaflet by adding the following wording: **Proposed change:** 'In case of pH adjustment and isotonisation with minimal amounts of sodium [not more than 0.154 mmol (or 3.54 mg) Na+ per ml solution] the reference for sodium salts can be omitted.'	Not accepted. See comment in response to same point by 3.
29-30	9	**Comment:** It would be helpful to the reader to have all key information (i.e. when the Q&A takes affect) contained within the Q&A rather than having to toggle between webpages. **Proposed change:** When one or several Q&As have been finalised, the new information in the ~~package leaflet~~ **product information** will be included in a revised annex of the guideline. **The new product information text, translated into all EU languages will be applicable only when included in the revised Annex.**	Accepted. The Q&A has been updated.
37-39	9	**Comment**: 37 -39 paragraph states that if sodium is the main ingredient of	Accepted with editorial changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the medicine, it is out of scope of this Q&A. See general comment relating to maximising utility of information for HCP/patients. See also comment on lines 156-157 & 163 relating to recommendations from EMA/PRAC/234960/2015 stating the new threshold includes active and/or excipient content. See also general comment relating to inclusion of contribution from diluent e.g. sodium chloride solution solution. **Proposed change:** '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)**, or in the preparation of the medicine prior to administration e.g. dissolution in sodium chloride solution prior to infusion**, and also as an excipient. ~~The former is out of scope of this Q&A.~~**The threshold limits and information for the physician and patient in the product information take into consideration the total dose of sodium taken with the medicine prior to administration.**'	
37-39	13	**Comment:** This paragraph does not match the title of section 2 "What is sodium and why is it used as an excipient?" It is rather more appropriate to present this information in section 3 "Which medicinal products contain sodium". The wording "the former" may be subject to multiple interpretations. Does it refer to the main ingredient (thus including both examples) or only to medicines that are intended to replace physiological sodium? It is anticipated that the first	Partly accepted. The paragraph has been moved and includes some minor editorial changes. In addition, the Q&A has been updated to make it clear that, as with the current guideline, the thresholds relate to total sodium i.e. active plus diluent plus excipient.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		interpretation applies. This would mean that the use of sodium as part of the active substance (e.g. sodium in sodium diclofenac) would be outside the scope of this document. This approach would need further explanation / discussion in the Q&A, especially as some active moieties can also be given through the use of other salts, or through formulations containing the base/acid form. Preferably, the use of sodium as part of the active substance is also included in the scope of this document. **Proposed change:** Move this paragraph to the beginning of section 3. Change text into "Sodium can be included in medicines in different forms. It can be used as the active therapeutic moiety itself e.g. Na in NaCL (table salt) to replace physiological sodium; as part of the active substance e.g. when an active moiety is presented as a sodium salt e.g. Na in sodium diclofenac; as the excipient moiety itself e.g. Na in NaCL to arrive at the correct osmolality of a parenteral solution or as part of the excipient e.g. sodium bicarbonate. The inclusion of sodium as the active therapeutic moiety itself is outside the scope of this Q&A."	
40	13	**Comment:** Clarify that the purpose of the sodium salt depends on the type of the overall excipient. **Proposed change :** "Excipients that are presented as sodium salts are most	Accepted.

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		commonly used to increase solubility. Other sodium containing excipients may be used for disintegration, chelation, lubrication, binding, emulsifying, stabilising, colouring or antimicrobial properties."	
44	13	**Comment:** Sodium can be found as excipient in other medicines than effervescent formulations effervescent as well. **Proposed change:** Change the wording into: "Sodium can be e.g. be found in effervescent, medicines. In such medicines "	Accepted.
48-50	13	**Comment:** This is duplication of the information that is already stated, e.g.: - sodium can be found in effervescent medicines (line 44), and - large quantities of sodium salts may be required to enhance solubility of a medicine (line 47). **Proposed change:** Revise the sentence "Large qualities" as follows "Also in other types of dosage forms, large quantities…." Remove the sentence "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."	Partly accepted. "Large quantities…" sentence revised as suggested. Retained the sentence: "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". Whilst this is implicit in the preceding text it is stated much more clearly here and is an important point.
52-55	13	**Comment:**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The reference to the UK list is not considered appropriate in the context of this Q&A and should be deleted. Health care professionals and users should rely on the information from their own NCA on the quantity of sodium in a medicine as 1) formulations may differ among countries even if from the same company; 2) the formulation of a medicinal product may change over time upon agreement from the NCA. In the latter situation, formulations with different sodium contents may be available to the market for a maximum of 5 years. The MEB acknowledges that some NCAs may not have information on the sodium content of medicines readily available to the public, however this is not a good excuse to refer to the UKMI. **Proposed change:** Delete line 52 to 55 "UK medicines… following issues". Replace by "The sodium content of a medicine is known to the regulatory authorities and marketing authorization holders 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"	
74-75	13	**Comment:** This is considered common knowledge and out of scope for this document. **Proposed change:** Remove the sentence "Risk was measured using a statistic known as the odds ratio and presented including a confidence	Not accepted (see below).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		interval which shows the range of risks that may be true."	
75-81	13	**Comment:** The description of results is too long and contains repetitive information, hampering readability of the conclusion. The results should be summarized in short with only the relevant information. **Proposed change:** Change the wording into: "The risk (odds ratio) of cases having had a high sodium content of medicine instead of a standard formulation of the same medicine was 1.16 (1.12 – 1.21) for non-fatal heart attack or a fatal cardiovascular condition, 1.22 (1.16 – 1.29) for non-fatal stroke and 7.18 (6.74 to 7.65) for hypertension."	Not accepted. We do not consider this to reflect the findings as accurately as the original text.
93	13	**Comment:** Please add the Odds Ratio (OR) **Proposed change:** "(…) was very strong **(OR: 7.18)**, and so is likely (…)".	Accepted.
94-95	13	**Comment:** There is no justification for this statement. **Proposed change:** Remove the sentence "This is supported by the fact that an association is already accepted to exist between high dietary sodium and cardiovascular events, especially hypertension."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
112-113	13	**Comment:** As this Q&A is a Union document, examples referring to a single national situation should be kept to the minimum and avoided where possible. This example does add little to the former sentence and can be deleted. **Proposed change:** Remove the sentence for example in the UK it is recommended for adults to have less than 6g of sodium chloride 112 per day (equivalent to less than 2.4g (or 104mmol) sodium per day).	Accepted.
120	13	**Comment:** Please replace carers with caregivers (rationale: somebody may care, but not give care; somebody may give care without caring).	Accepted
124	13	**Comment:** Consider starting this sentence with the word "therefore". This is because other tools that the product information may be adopted to reach this goal, however such other tools are little excuse to refrain from adequate information in the product information. **Proposed change:** Therefore, …….	Partly accepted. Minor editing change.
130	13	**Comment:** Please consider other caregivers as well.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "(…) patients, ~~and~~ parents **and other caregivers** as being part of (…)"	
134	13	**Comment:** Please clarify if the dose refers to the single or maximum dose. **Proposed change:** "with more than 1 mm of sodium per single dose…."	Accepted
143-144	13	**Comment:** This paragraph is part of the list of concerns presented in bullet points. **Proposed change:** Please add a bullet for this sentence.	Accepted
156-157 163	9	**Comment:** The threshold for sodium content of 20% of the WHO recommended maximum daily intake for sodium is based on content from active and/or excipients (see EMA/PRAC/234960/2015 Recommendation p.7 line 15-16). The Excipient guideline thresholds are, except where otherwise stated, expressed as Maximum Daily Doses **of the excipient only**. As appropriate the preparation for the medicine prior to administration e.g. dissolved in sodium chloride solution should be considered, together with duration and frequency of	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		administration. **Proposed change:** Additional text to add as appropriate to column 'Information for the Package Leaflet'. - For proposed revisions to the table, as presented in this comments table, refer to the last page of this document:	
		'<After dilution for use,>' Additional text as a footnote to this row for 'Sodium': 'Sodium threshold relates to total content of sodium e.g. from active ingredient, excipients and any diluent required in the SmPC prior to administration.'	Partially accepted. All footnotes have been deleted and the information made clear in the Q&A document and the comments column.
		For the ≥ 17mmol threshold comment column: 'As a general guidance, this threshold applies to long term use or regular exposure where long term use is to be considered as continuous daily use for > 1 month and regular exposure is to be considered repeated use for more than 2 days every week.'	Accepted with editorial changes to shorten the statement.
160-161	9	**Comment:** The frequency and duration of administration should be added. (See EMA/PRAC/234960/2015, p.7 from line 24) **Proposed change:** '…salt in their diet. The criteria for formulations that warrant update of the product information are: • ≥ 17mmol sodium in the maximum daily dose, and	Accepted with minor editing revisions.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• are for long term use and regular exposure. As a general guidance, long term use is to be considered as continuous daily use for > 1 month and regular exposure is to be considered repeated use for more than 2 days every week.'	
161	3	**Comment:** The dosage of medicines dosed based on body weight, body surface area or indication can vary a lot. Thereby the medicine or rather the sodium content, that has to be declared, can reach different values. Depending on the sodium content of the individual dose different information has to be included in the package leaflet. This will impair readability and may confuse the patient. For example: Some examples for the treatment with Methotrexate 25 mg/ml solution for injection: recommended dosages (BSA 1,8 m^2): -low-dose therapy - single dose under 100 mg/m^2: Declaration of sodium content: The dose of 100 mg/m^2 Methotrexate contains 34.57 mg sodium per dose. This is equivalent to 1.73% of the recommended maximum daily intake of sodium for an adult. -medium-dose therapy – single dose between 100 mg/m^2 - 1,000 mg/m^2 :	Accepted. It is clear that some flexibility in the best way of expressing sodium content is required for parenterals that have variable dosing regimens. The Q&A has been updated to state that for parenterals the amount of sodium should be expressed in mg per vial.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Declaration of sodium content: The sodium content can vary between 34.57 - 345.70 mg per dose. This is equivalent to 1.73-17.28% of the recommended maximum daily intake of sodium for an adult. -high-dose therapy – single dose above 1,000 mg/m² In CNS localised Non-Hodgkin's lymphoma doses between 1,500 – 4,000 mg/m² are/were given. Declaration of sodium content: The sodium content can vary between 518,55 – 1382,80 mg sodium per dose. This is equivalent to 25.93 – 69.14% of the recommended maximum daily intake of sodium for an adult. **Proposed change:** Medicine with different dosages based on body weight or body surface area or with different dosages depending on the indication should be specified per vial content.	
163	1	**Comments:** The proposed warning to contact the pharmacist or doctor in case of prolonged use of a medicinal product with high sodium content could discourage patients to take the medicinal product and/or jeopardize the intake compliance. These risks may far outweigh possible (or questionable) benefits for patients being advised talking to pharmacists or doctors concerning the high	Not accepted. If the patient is regularly taking a high sodium medicine for a prolonged period they should discuss the possible risk with a HCP who may be able to either reassure them or suggest a low sodium alternative, depending on their individual circumstances. For those on a salt-restricted diet or with high cv risk including this information is of clear benefit to

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sodium content of the medicinal product. In the light of the new and actual paradigm of "better regulation" or "REFIT" (Regulatory Fitness and Performance Programme) in EU law-making processes it seems counterproductive to complicate information on medicinal products without clear benefit for the patients. **Proposed change:** Omission of the warning "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."	the patient.
163	2	**Comments:** Concerning the concentration of 1 mmol (23mg per dose), do patients who follow a low-salt diet require special care? If so, please indicate in the package leaflet which precautions or special care patients following low-salt diets should take.	Not accepted. One of the reasons for introducing an additional threshold was that patients taking medicines with low levels of sodium (~1% of the WHO allowance) were being unnecessarily advised to take the sodium content into consideration if they were on a low salt diet. It is unlikely that an otherwise healthy patient would need to take any action if they take a product that delivers between 1% and 20% of their daily recommended dietary sodium in the max daily dose.
163	3	**Comment:** We suggest to exempt products containing sodium just for pH adjustment and isotonization completely from the obligation to inform patients in the package leaflet.	Not accepted. It is helpful for patients to be reassured about a low sodium content of their medicine. Where the addition of a sodium-containing diluent is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Erase the sentence: ~~This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. it is essentially "sodium-free".~~ In case of pH adjustment and isotonisation with minimal amounts of sodium [not more than 0.154 mMol (or 3.54 mg) Na+ per ml solution] the reference for sodium salts can be omitted.'	specified in the SmPC, this should be taken into account when calculating the overall sodium content.
163	3	**Comment:** There is a mistake in the calculation: 1 mmol of sodium (Na) = 58.4 mg table salt. **Proposed change:** 1 mmol of sodium (Na) "23 mg Na = ~~**57**~~**58.4** mg table salt (NaCl).	Accepted.
163 Column "threshold"	3	**Comment:** The thresholds are expressed inaccurate: - less than 1 mmol **per dose** - 1 mmol **per dose**. It is not clear (without indication of more or less). It would be better to write « between 1 mmol and 17 mmol per dose » - 17 mmol in the **maximum daily dose**. It is not clear (without indication of more). It would be better to write « more than 17 mmol per dose». Furthermore, it is expressed in the maximum daily dose and not per dose.	Not accepted. The Excipient Guideline explains what the thresholds relate to ("The threshold is a value, equal to or above which it is necessary to provide the information stated"). It is not accepted that the threshold needs to relate to the same units and is not how they have been calculated. Thus the ≥1mmol threshold relates to the amount of sodium per dose - this allows patients to easily calculate how much sodium they are taking per day. The ≥17mmol threshold relates to the amount of sodium in the maximum recommended daily dose – this informs

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		We have to express all the thresholds using the same units, either **per dose**, either in **the daily dose**. **Proposed change:** **Between** 1 mmol (23 mg) **and 17 mmol (391 mg)** per dose **More than** 17 mmol (391 mg) **per dose** ~~in the maximum daily dose~~	patients who are taking the maximum recommended dose they are consuming more than 20% of the WHO daily recommended allowance.
163-164	4	**Comment:** For the following thresholds a) 1 mmol (23 mg) per dose and b) 17 mmol (391 mg) in the maximum daily dose clarification is needed for the equivalent <Y%> of the recommended maximum daily intake of sodium in children. Although there is a comment that "This is also relevant for children, where the maximum daily intake is considered to be proportional to adults and based on energy requirements" it is our opinion that further clarification is required how this would be translated in actual terms and % for paediatric patients. Age ranges for children may also be required in order to clarify fully. The age ranges applicable will need to be clarified by the EMA. **Proposed change :** 1 mmol (23 mg) per dose: One dose of this medicinal product contains <X mg> sodium	Not accepted. The cardiovascular risk from sodium exposure in older children is not as clearly defined as in adults. Furthermore it must be borne in mind that the thresholds are empirical. Providing more definitve thresholds for children has been considered in detail and because of the substantial between children in their energy requirement (and thus salt tolerance) due to differences in size/weight, levels of activity etc for children of the same age it was considered not possible to provide more defined age-specific thresholds for children. For children, the greatest risk with sodium comes from acute exposure to high doses in newborns. Medicines with relevant paediatric indications and high sodium content already include warnings about the risk of hypernatraemia, especially in those with renal impairment. The Q&A makes it clear any pre-existing warnings on sodium should be retained.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(found in table salt). This is equivalent to <Y%> of the recommended maximum daily intake of sodium for an adult. **For children (age ranges) this is equivalent to <Y%> of the recommended maximum daily intake of sodium.** 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. **For children (age range) this is equivalent to <Y%> of the recommended maximum daily intake of sodium.** 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.	
163	5	**Comment:** In the comment field for medicinal products containing **> 1 mmol (23 mg) sodium per dose** a reference to the WHO recommended daily dose is missing. According to the Q&A document there is no consistent recommended daily intake of sodium in the EU. It would therefore be beneficial to include a reference to the WHO recommendation, because patient may by default refer the percentage to their national (potentially deviating) recommendations. **Proposed change:**	Partly accepted. The Q&A and the comments column have been updated with respect to the WHO daily dose of sodium. Reference to cooking salt has not been added as this information is not for patients and in any case the only information that is essential to know in this context is the amount of sodium/day.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Inclusion of a reference to the WHO recommended daily dose in the column "comments" for medicinal products containing **> 1 mmol (23 mg) sodium per dose**, e.g. ***The recommended maximum daily intake of sodium for an adult refers to that given by the WHO. The WHO recommends adults to consume less than 5g of sodium chloride (table salt) per day (equivalent to less than 2g (or 87 mmol) sodium per day).***	
163	5	**Comment:** As stated in line 111-112 of the Q&A document individual countries have their own guidance regarding the maximum recommended daily dose for sodium. In order to avoid confusion of the consumer Mylan EPD is of the opinion that the WHO reference should be included in the proposed PIL wording, as patients may by default refer the percentage to their national recommendations. This applies to both, medicinal products containing **> 1 mmol (23 mg) sodium** and medicinal products containing **> 17 mmol (391 mg) sodium** per dose. **Proposed change:** […] This is equivalent to <Y%> of the **WHO** recommended maximum daily intake of sodium for an adult.	Not accepted. It is not usual practice to refer to an independent body in the PL and some patients may not recognise the WHO. Moreover, the PL states what percentage of the daily recommended sodium intake is in a dose, based on the WHO recommendations and so explicit mention of WHO is not necessary. Even if patients think the value is a percentage of their national guideline (if one exists) the absolute value is not what is important – it is the percentage and what threshold category it falls into. The advice that it either considered acceptable or that they should see a doctor is what is important.
163	5	**Comment:** The term "per dose" given in the table for defining the threshold for medicinal products containing **> 1 mmol (23 mg) sodium**	Partly accepted. The term "dose" has been clarified in the threshold column.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and medicinal products containing **less than 1 mmol sodium** is not clear. Does this means "one single dose", the "maximum single dose" or the "maximum daily dose"? **Proposed change:** A definition of the term "per dose" should be included in the comment fields of the table in order to avoid misinterpretation.	
163	5	**Comment:** The proposed PIL wording for medicinal products containing **less than 1 mmol per dose** is as follows: This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. it is essentially 'sodium- free'. The term "per dose" should be further defined in order to avoid misinterpretation. **Proposed change:** This medicinal product contains less than 1 mmol sodium (23 mg) per <**single** dose**, e.g. tablet**>, i.e. it is essentially 'sodium- free'.	Partially accepted. The term <dose> has been clarified in the PIL text.
163	5	**Comment:** The proposed PIL wording for medicinal products containing **> 1 mmol (23 mg) sodium** is as follows: One dose of this medicinal product contains <X mg> sodium (found in table salt). […] The term "one dose" should be further defined in order to avoid	Partly accepted. Providing an equivalent amount of sodium in terms of mg of cooking salt is not helpful as most people would be unable to visualise how much this was. A proportion of the maximum recommended daily dietary intake is considered more useful.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		misinterpretation. The addition "found in table salt" is not clear. If the user doesn't know already that sodium is a part of table salt, he may now think of sodium being a separate substance in table salt. A reference to the corresponding amount of table salt may be more helpful. **Proposed change:** One **<u><single</u>** dose**<u>, e.g. "tablet"></u>** of this medicinal product contains <X mg> sodium (~~found~~ **<u>equivalent to the amount of sodium</u>** in **<u><Z> mg</u>** table salt). […]	
163 Column "comments"	5	**Comment:** According to the PRAC recommendation on signals dated 23rd April 2015 (EMA/PRAC/244960/2015), an update of the labelling of medicines is required to make the sodium content clearer for patients and healthcare professionals. **A wording is proposed for SmPC section 4.4, PIL section 2 and Label** and it is stated that the Excipient Guideline will be updated with the new sodium-labelling requirements accordingly. In order to ensure that the correct wording is implemented in the product information of all concerned products it would be advisable **to include the SmPC and Label wording in the comment field of the table** as well. **Proposed change:** Comment field for medicinal products containing **> 17 mmol (391 mg) sodium** in the maximum daily dose:	Reference to SmPC wording is proposed in the comments column of the Q&A. However, the proposed SmPC wording is partly accepted. The comments column refers to the PRAC recommendation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed SmPC wording: *Section 4.4* *This medicinal product contains <X mg> sodium per single dose, equivalent to <Y%> of the WHO recommended maximum daily intake for sodium for an adult.* *The maximum daily dose of this product is equivalent to <Z%> of the WHO recommended maximum daily intake for sodium.* *[Product name] is considered high in sodium. This should be particularly taken into account for those on a low salt diet.* *Proposed Label wording:* *High in sodium – see leaflet for further information.*	
163	5	**Comment:** In the PRAC recommendation on signals dated 23rd April 2015 (EMA/PRAC/244960/2015) the following is mentioned: *Having considered the available evidence in the literature, the PRAC agreed that the MAHs with formulations that meet the criteria listed below, should submit a variation following the publication of the updated Excipient Guideline, at the subsequent routine regulatory opportunity or within 12 months, whichever is sooner.* ***Criteria for formulations that warrant update of product information*** *1. ≥ 17mmol sodium in the maximum daily dose and that*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		2. Are for long term use or regular exposure.	
		In the Q&A document on sodium the second criterion, i.e. "long term use or regular exposure" is not respected. As a consequence, the new proposed PIL wording is applicable to all medicinal products containing **> 17 mmol (391 mg) sodium** in the maximum daily dose. Mylan EPD sees this with concern, especially due to the second paragraph of the proposed PIL wording: *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.*	Accepted. Applying the high dose warning only to those products for long terms use or regular exposure is now made clear in the Q&A and comments column. This is consistent with the PRAC recommendation.
		The wording "*for a prolonged period of time*" should be avoided in the PIL of medicinal products indicated for short time use only. This is relevant for safety and liability reasons, especially due to the fact that "*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***" as stated in the Q&A document. It should also be mentioned that the PRAC recommendation defines "regular exposure" as "repeated use for more than 2 days every week" which would not be in line with the term "daily basis" as proposed in the Q&A document. In order to avoid misinterpretation by the consumer the proposed PIL wording should be either adapted (deletion of "*for a prolonged period of time*") or restricted to those medicinal products which are high in sodium content (≥ 17mmol sodium	Partially accepted. Only products that have a sodium content of more than 17mmol per max daily dose and whose indications or posology allow for regular or continuous use are included within the scope of this exercise. Any OTC medicines whose posology does not allow for such use will not need to include this warning.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		in the maximum daily dose) and **indicated for long term use or regular exposure** as recommended by the PRAC. In the latter case the information for the Package leaflet should be amended to better reflect that regular exposure without daily intake is also in scope.	
163-164 Column "inform-ation for the PL"	6	**Comment:** Generally, in the PL, "medicine" is to be used, instead of "medicinal product" according to QRD recommendation (please refer to document EMA/57325/2011 rev. 8#) **Proposed change (if any):** Amendment at three locations of the proposed information in the PL recommended.	Accepted.
163-164	6	**Comment:** Since units of mmol neither may be meaningful to patients nor prescribers, the units of mmol should be deleted also in the category of "Less than 1 mmol per dose". **Proposed change (if any):** PIL wording: "This medicine contains less than 23 mg sodium per <dose>, i.e. it is essentially 'sodium-free'."	Partially accepted. For the <1mmol threshold reference to "mmol" was retained as per current guidance.
163-164	6	**Comment:** <dose> should stand for "dosage form unit", such as per tablet, per capsule, per vial or per ml oral solution.	Partially accepted. Dosage unit/volume has been included to make it clear to implementing MAHs.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Regarding all threshold categories of sodium, the PIL wording should name the amount of sodium per "dosage form unit", such as per tablet, per capsule, per vial or per ml oral solution since with some medicinal products dose ranges are approved. **Proposed change (if any):** PIL wording: Under the category "1 mmol (23 mg) per dose" in should be read as follows: "One <dose> of this medicine contains <X mg> sodium…"	
163-164	6	**Comment:** In the category of "17 mmol (391 mg)…" sodium, the amount of sodium should be stated per dose unit (<dose>), as in the other threshold categories, since for patients the amount of sodium per maximum daily dose may be irrelevant if they take/use lower doses. **Proposed change (if any):** PIL wording: Under the category of "17 mmol (391 mg) in the maximum daily dose" the Information in the PL should be read as follows: "One <dose> of this medicine contains <X mg> sodium…"	Partially accepted. The amount of sodium per tablet is now provided which will enable patients to calculate how much sodium they are taking per day - if this is less than the maximum dose. Based on another comment, we have also proposed that MAHs include the number of doses that would be needed to reach the 17mmol threshold.
163-164	6	**Comment:** The wording in brackets, i.e. "…(found in table salt)." should be	Not accepted. This wording has been changed in line with another comment

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		amended to "…(also found in table salt)." at both locations. **Proposed change (if any):** PIL wording: Under both categories "1 mmol (23 mg) per dose" and "17 mmol (391 mg) in the maximum daily dose" it should be read as follows: "One <dose> of this medicine contains <X mg> sodium (also found in table salt)."	to "(main component of cooking salt)."
163-164	6	**Comment:** It should be indicated that the percentage of the recommended maximum daily intake of sodium for an adult is based on the WHO recommendation, the more so since – as mentioned in the question and answer document, section 4 - "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)". **Proposed change (if any):** PIL wording: "This is equivalent to <Y%> of the maximum daily intake of sodium for an adult, as recommended by the World Health Organization (WHO)."	Not accepted. The sentence in the Q&A has been deleted but the document and the comments column have been updated with respect to the WHO daily dose of sodium.
163-164	6	**Comment:** The comments for both threshold categories "1 mmol (23 mg) per dose" and "17 mmol (391 mg) in the maximum daily dose" should contain the WHO adult recommended maximum daily dietary intake for sodium in order to allow	Accepted with editorial changes.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>exact calculation of the percentage of the WHO adult recommended maximum daily intake of sodium.

Proposed change (if any):

Comment under both threshold categories “1 mmol (23 mg) per dose“ and “17 mmol (391 mg) in the maximum daily dose” should contain the information that “WHO recommends intake of < 2 g sodium (< 5 g table salt) per day in adults.”</td><td></td></tr>
<tr><td>163-164</td><td>6</td><td>Summary of recommendations regarding the proposal for an updated information in the package leaflet
<table>
<tr><th>Name</th><th>Route of Administra-tion</th><th>Threshold</th><th>Information for the Package Leaflet</th><th>Comments</th></tr>
<tr><td rowspan="2">Sodium</td><td>Parenteral</td><td>Less than 1 mmol per dose</td><td>This medicine contains less than 23 mg sodium per <dose>, i.e. it is essentially ‘sodium- free’.</td><td>1 mmol of sodium (Na) = 23 mg Na = 57 mg table salt (NaCl).</td></tr>
<tr><td>Oral

Parenteral</td><td>1 mmol (23 mg) per dose</td><td>One <dose> of this medicine contains <X mg> sodium (also found in table salt). This is equivalent to <Y%> of the maximum daily intake of sodium for an adult, as recommended by the World Health Organization (WHO).</td><td>WHO recommends intake of < 2 g sodium (< 5 g table salt) per day in adults.</td></tr>
</table></td><td>See above for individual comments on proposals.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome

	Oral Parenteral	17 mmol (391 mg) in the maximum daily dose	One <dose> of this medicine contains <X mg> sodium (also found in table salt). This is equivalent to <Y%> of the maximum daily intake of sodium for an adult, as recommended by the World Health Organization (WHO). 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> <or> <your child> <have> <has> been advised to follow a low salt diet.	WHO recommends intake of < 2 g sodium (< 5 g table salt) per day in adults. 17 mmol (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.

163 | 7

Comment:

For Threshold "1 mmol (23 mg) per dose" we suggest to put "One dose" in brackets in column "information for the Package leaflet" to indicate that "one dose" is to be replaced by a precise information, e.g. 1 tablet or 25 ml solution.

Since one dose is not clearly defined, especially for liquid dosage forms, it is necessary to give precise information at this point.

Proposed change:

Name	Route of Administra-tion	Threshold	Information for the Package Leaflet	Comments
Sodium	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.	

Accepted but with editorial changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
163	7	**Comment:** In our opinion, the proposed wording for oral/parenteral products containing 17 mmol (391 mg) or more sodium in the maximum daily dose might be confusing for the patients. The declaration of the amount/intake of sodium based on the **maximum recommended daily dose** might lead to a misinterpretation of information by the patient because: • The maximum recommended daily dose can vary depending on the indication. Hence, a patient might take/use the maximum recommended daily dose for one of the indications but still takes/uses less than 17 mmol (391 mg) of sodium. • The physician may recommend an individual maximum daily dose for a patient for example due to co-medications or renal/hepatic dysfunction, which is lower than the maximum daily dose mentioned in the leaflet. The wording does not contain usable information for the patient. **In our opinion the information in the leaflet should enable the patient to decide:** Do I reach the critical threshold of sodium intake so that I have to contact the pharmacist/doctor? Therefore, we suggest to base the information regarding the amount/threshold of sodium upon one dose and to include the information that patients should talk to the pharmacist/doctor when they reach/exceed the threshold of 17 mmol (391 mg) by taking/using <Z doses>.	Accepted. This is a good suggestion that enables a patient who is taking fewer than the maximum daily recommended doses of a medicine to know how many tablets they need to take before the threshold is reached.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>Proposed change:
<table>
<tr><th>Name</th><th>Route of Administration</th><th>Threshold</th><th>Information for the Package Leaflet</th><th>Comments</th></tr>
<tr><td>Sodium</td><td>Oral Parenteral</td><td>17 mmol (391 mg) in the maximum daily dose</td><td><One ~~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) <Z doses> or more of [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.</td><td>17 mmol (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.
<Z doses> has to reflect the lowest number of doses for which the threshold of 17 mmol (391 mg) of sodium is reached/ exceeded.</td></tr>
</table></td><td></td></tr>
<tr><td>163</td><td>8</td><td>Comment:

The proposed labelling changes should be restricted to those medications, where the knowledge of the sodium content relative to the WHO recommendation could be of any use for a patient (i.e. patients on a low sodium diet).

Therefore, it is proposed not to change the labelling for parenteral drugs, as parenteral drugs are administered by Healthcare Professionals, or administered following close advice from HCPs.

Proposed change:</td><td>Not accepted.

The existing advice for parenterals and oral products containing more than 1mmol sodium was felt to be too crude a threshold and that patients on low salt diets would not need to take care when taking medicines with such levels. For this reason the ‘high’ sodium threshold was introduced. This will apply to both oral and parenteral products.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Parenteral drugs Column 2, Row 2+3 of table: Oral Add: 4th Row for "Parenteral" with the unchanged text from 2003 Guideline (columns 2-4): "Parenteral; 1 mmol (23 mg) 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	8	**Comment:** The proposed labelling changes should be restricted to those medications, where the knowledge of the sodium content relative to the WHO recommendation could be of any use for a patient (i.e. patients on a low sodium diet). **Proposed change:** Oral drugs column 4, row 2 of table: "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.~~ **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."**	Not accepted. The threshold for adding a warning for patients on a low salt diet is only thought relevant where the max daily sodium exposure exceeds 17mmol.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
163	8	**Comment:** The proposed labelling changes should be restricted to those medications that are intended for regular/long term use. **Proposed change:** Oral drugs Column 3, Row 3 of table: Add: "If according to labelled posology the product has to be taken on a daily basis for more than 1 month or repeated use for more than 2 days every week for more than 1 month."	Partly accepted. A slightly modified form of the proposed wording has been added to the comments column.
163 Column "threshold"	8	**Comment:** The thresholds are not expressed correctly: ▪ less than 1 mmol **per dose**: OK ▪ 1 mmol **per dose**: it is not clear (without indication of more or less). It would be better to write "between 1 mmol and 17 mmol per dose" ▪ 17 mmol in the maximum **daily dose**. It is not clear (without indication of more). It would be better to write "more than 17 mmol per dose". Furthermore, it is expressed in the maximum daily dose and not per dose. In addition, we would suggest expressing all the thresholds using the same units, either **per dose**, either in **the daily dose**.	Partly accepted. Text has been updated with respect to expressing thresholds in terms of <dose>. However, the thresholds relate to different units i.e. single <dose> vs <maximum daily dose> to provide the most useful information to the patient. The explanatory note in the Excipient Guideline makes it clear what the thresholds relate to.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
163	9	**Comment:** Current wording could be made more patient friendly. Text related to mmol sodium amended to make it consistent with the 1 mmol and 17 mmol thresholds. **Proposed change:** ~~This medicinal product~~ One dose of this medicine contains less than ~~1 mmol sodium (~~23 mg~~)~~ sodium (found in table salt)~~per <dose>~~, ~~i.e~~. it is essentially 'sodium-~~-~~free'.	Partly accepted. The text is essentially unchanged from that in the current Excipient guideline. Medicinal product has been changed to medicine.
163	9	**Comment:** Current wording could be made more patient friendly. **Proposed change:** One dose of this ~~medicinal product~~ medicine contains <x mg> sodium (found in table salt). This is equivalent to <Y%> of the recommended maximum daily intake of sodium for an adult.	Partially accepted with editorial changes.
163	9	**Comment:** Current wording could be made more patient friendly. **Proposed change:** The maximum recommended daily dose of this ~~medicinal product~~ medicine 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~~ <doctor> <or> ~~doctor~~ <pharmacist> if <you> <or> <your child> need(s) [product name] on a daily	Not accepted. This warning has been changed to inform the patient how many <doses> they need to take to reach the threshold, in line with other comments received. Most patients would be advised to follow a low salt diet.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		basis for a prolonged period of time, especially if <you> <they> have been advised to follow a low sodium (salt) diet.	
163	9	**Comment:** Propose addition of WHO sodium DDI to assist with the inclusion of the % DDI sodium for the 1 mmol and 17 mmol thresholds. **Proposed change:** The WHO recommended maximum daily dietary intake for sodium is 2 g/day (equivalent to 5 g/day of table salt). 17 mmol (391 mg) is approximately 20% of the WHO adult recommended maximum daily dietary intake for sodium and is considered to represent 'high' sodium.	Accepted with editorial changes.
163	9	**Comment:** "...This is also relevant for children, where the maximum daily intake is considered to be proportional to adults and based on energy requirements..." It may be more helpful to parents/carers to have definitive values for children, particularly for medicines developed for exclusive use in the paediatric population.	Not accepted for the reasons given above.
163 (Row 1 - Table on Page 7)	9	**Comment:** As stated in the general comment for parenteral products which very often have body weight based dosing it is not always possible to estimate the amount of sodium per dose as it varies according to patient. Should "dose " be stated as "<dose>" as is currently in the 2003 guideline so that in the above instance	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the amount of sodium per vial can be quoted. **Proposed Change (marked in red) under the column with the heading "Threshold*":** Less than 1mmol per **<**dose**>**	
163 (Row 2 - Table on Page 7)	9	**Comment:** As stated in the general comment for parenteral products which very often have body weight based dosing it is not always possible to estimate the amount of sodium per dose as it varies according to patient. Should "dose " be stated as "<dose>" as is currently in the 2003 guideline so that in the above instance the amount of sodium per vial can be quoted. **Proposed Changes (marked in red) under the column with the heading "Threshold*":** 1 mmol (23 mg) per **<**dose**>**	Accepted.
163 (Table on Page 7)	9	**Comment:** There is a clear guidance given when the product contains less than 1mmol sodium per dose, for 'parenteral' route of administration with a statement that needs to be included in the package leaflet. For 'oral' products however, one may conclude that nothing needs to be reported regarding sodium on the label if the threshold is less than 1 mmol sodium per dose. There is no clear guidance given currently in the table. **Proposed change:**	Accepted. The Q&A is now clear that the same statement as for parenterals should be included for oral products that contain <1mmol sodium per dose.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Identify in the table by adding a new row for products with 'oral' route of administration with a sodium threshold of 'less than 1 mmol per dose'. In this instance, if a statement is not required in the package leaflet it could be stated as 'no statement is required for the leaflet'.	
163 (Row 2- Table on Page 7)	9	**Comment:** Suggestions for improved clarity of the proposed package leaflet wording, when the threshold is 1 mmol (23 mg) per dose, in Oral and Parenteral route of administration. **Rationale:** "Table salt" is ambiguous. Patients may wonder if this also applies to cooking salt, rock salt or salt already in (processed) food. **Proposed Text Changes (marked in red) for the column with the heading "Information for the Package Leaflet" :** ~~One dose of t~~ This medicinal product contains <X mg> sodium (found in ~~table~~ salt) per <dose>. This amount is equivalent to <Y%> of the recommended maximum daily intake of sodium for an adult.".	Partly accepted. Alternatives to table salt have been widely debated and table salt considered least ambiguous and most widely recognised. We prefer to start the sentence with the unit dose (as suggested in other comments). "Amount" has been added.
163 (Row 3- Table on Page 7)	9	**Comment:** Suggestions for improved clarity of the proposed package leaflet wording, when the threshold is 17 mmol (391 mg) in the maximum daily dose, in Oral and Parenteral route of administration.	Not accepted. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Rationale: "Table salt" is ambiguous. Patients may wonder if this also applies to cooking salt, rock salt or salt already in (processed) food. **Proposed Text Changes (marked in red) for the column with the heading "Information for the Package Leaflet"**: The maximum recommended daily dose of this medicinal product contains <X mg> sodium (found in ~~table~~ salt). This amount is equivalent to <Y%> of the recommended maximum daily intake of sodium for an adult.	
Line 163-164	9	**Comment:** The proposed labelling changes could be restricted to those medications, where the knowledge of the sodium content relative to the WHO recommendation could be of any use for a patient (i.e. patients on a low sodium diet). **Proposed change:** Parenteral drugs Column 2 , Row 2+3 of table: Oral Add: 4th Row for "Parenteral" with the unchanged text from 2003 Guideline (columns 2-4): "Parenteral; 1 mmol (23 mg) 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	Not accepted – for the reasons provided above on the need for an additional 'high' sodium threshold.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		diet."	
Line 163-164	9	**Comment:** The proposed labelling changes could be restricted to those medications, where the knowledge of the sodium content relative to the WHO recommendation could be of any use for a patient (i.e. patients on a low sodium diet). **Proposed change:** Oral drugs column 4, row 2 of table: "One dose of this medicinal product contains <X mg> sodium (found in 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."	Not accepted. See previous comment to same proposal
163-165 Column "threshold"		**Comment:** The *note at the bottom of the table which states that '*The threshold is a value, equal to or above which it is necessary to provide the information stated*.' is not sufficiently prominent. The sodium action thresholds should be displayed with the notes included. This is already the case for ethanol in the Annex of the guideline (page 9). The thresholds are displayed as 1) *Less than 100mg per dose* and 2) *100mg- 3g per dose*, and 3) *3g per dose*.	Not accepted. Thresholds are explained in the explanatory notes of the Excipient Guideline. We do not consider it necessary to include a positive statement about being safe to use in patients on a low salt diet (and think this could be open to misinterpretation) – saying it is essentially sodium-free is sufficient. It is the role of the HCP to advise on the safe use of a medicine in any individual patient.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Threshold column: Less than 1mmol per dose ~~1 mmol (23 mg) per dose~~1 to x? mmol per dose Greater than or equal to 17 mmol (391 mg) in the maximum daily dose Delete footnote to table: '~~* Note: The threshold is a value, equal to or above which it is necessary to provide the information stated [1].~~' Information on the package leaflet for less than 1 mmol per dose threshold: This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. it is essentially 'sodium- free' and can be used by people on a low sodium diet.	
163	9	**Comment:** The proposed labelling changes should be restricted to those medications that are intended for regular/long term use. **Proposed change:** Oral drugs Column 3, Row 3 of table: Add: "If according to labeled posology the product has to be taken on	Partly accepted. A note has been added to the comments column.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a daily basis for more than 1 month or repeated use for more than 2 days every week for more than 1 month."	
163	9	**Comment:** Comment concerning parenteral drugs containing less than 1 mmol per "dose" As mentioned in the comment above, mentioning that "*This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. it is essentially `sodium-free.´* might potentially confuse the patients reading the package leaflet.	Not accepted – wording for parenteral drugs containing <1mmol sodium has not materially changed.
		HCPs always carefully advice their patients in how to use the medicines. Thus, the exact information about sodium content should only be included in the SmPC, as information to the HCPs, not in the package leaflet. It could be included in section 2 of the SmPC.	Partly accepted. SmPC wording is now included in the comments column. However, information should always be provided to patients to allow them to make an informed decision about their medicine. Stating that a medicine is essentially sodium-free is more important now that PILs for all other medicines will include information on the total sodium content in Section 2.
		The information in the package leaflet should be as short and yet informative as possible. Thus it is proposed just to write that "*This medicine is "essentially `sodium-free´*. This will avoid any patient confusion about sodium content. Furthermore, we do not agree to include the sentence "….*and can be used by people on a low sodium diet"* in the package leaflet, as this advice should be given by the HCPs, not the MAH.	Not accepted. The shorter proposal does not link sodium with cooking salt for patients who are not aware. Comment: We agree it is the role of the HCP to advise patients and are not proposing to advise patients they can use a medicine if they are on a low sodium diet.
163	10	**Comment:** We suggest to exempt products containing sodium just for pH	Not accepted. Any sodium present in diluent or added by the user as

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		adjustment and isotonization completely from the obligation to inform patients in the package leaflet. **Proposed change:** Erase the sentence: ~~This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. it is essentially "sodium free".~~ **~~In case of pH adjustment and isotonisation with minimal amounts of sodium [not more than 0.154 mMol (or 3.54 mg) Na+ per ml solution] the reference for sodium salts can be omitted.'~~**	specified in the SmPC should be taken into consideration.
163	10	**Comment:** There is a mistake in the calculation: 1 mmol of sodium (Na) = 58.4 mg table salt. **Proposed change:** 1 mmol of sodium (Na) " 23 mg Na = ~~57~~**58.4** mg table salt (NaCl).	Accepted.
163 Column "threshold"	10	**Comment:** The thresholds are expressed inaccurate: - less than 1 mmol **per dose** - 1 mmol **per dose**. It is not clear (without indication of more or less). It would be better to write « between 1 mmol and 17 mmol per dose » - 17 mmol in the **maximum daily dose**. It is not clear (without	Not accepted. For reasoning see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		indication of more). It would be better to write « more than 17 mmol per dose». Furthermore, it is expressed in the maximum daily dose and not per dose. We have to express all the thresholds using the same units, either **per dose**, either in **the daily dose**. **Proposed change:** Between 1 mmol (23 mg) and 17 mmol (391 mg) per dose More than 17 mmol (391 mg) per dose ~~in the maximum daily dose~~	
line 163 (Table 5)	11	The comments in line 163 may still be incorporated in order to guide the prescriber with respect to its proportion of the WHO maximum recommended daily dietary intake for sodium.	Accepted. The amount of sodium in the WHO maximum recommended daily dose has been added to the SmPC wording in the comments column to enable prescribers to calculate how much sodium patients are ingesting through their daily dose of medicine.
163	11	• We propose to update the information to be added in the package leaflet concerning sodium intake for oral and parenteral route of administration as follows: • This medicinal product contains < X mg of sodium (found in table salt)/{dosage unit of pharmaceutical form}> < X mmol of sodium (found in table salt)/{dosage unit of pharmaceutical form}> < X mg of sodium (found in table salt)/mL> < X mmol of sodium (found in table salt)/mL> equivalent to <Y% of sodium/{ dosage unit of pharmaceutical form}> <Y% of sodium/mL> of the recommended maximum daily intake of	Partly accepted. Instructions for expression of sodium have been clarified. The sets of wording for thresholds >1mmol only are not always mutually exclusive – both could apply. As an example, for products with between 23 - 391mg sodium per dose, a patient may end up ingesting less than or greater than 17mmol, depending on the number of doses they take in a day.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sodium. Depending on your body weight and your dose of [product name]: • -<You <or> <your child> will receive less than <23 mg> per <day> (less than 1.1% of the recommended maximum daily intake of sodium). This medicinal product is considered as "sodium-free".> <or> • -<You <or> <your child> will receive between <23 mg> and <391 mg> per <day> (between 1.1% and 20% of the recommended maximum daily intake of sodium). <or> • -<You <or> <your child> will receive more than <391 mg> per <day> (more than 20% of the recommended maximum daily intake of sodium). This medicinal product is considered as having a "high" sodium content. 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>.	
line 163 (Table 5)	11	**Comment:** Current: 1 mmol (23 mg) **Proposed change:** ≥ 1 mmol (23 mg) < 17 mml/l (391 mg)	Not accepted. The two thresholds relate to two different units (single dose and maximum daily dose respectively) so cannot be combined into a single threshold.
163	11	**Comment:** Current: 17 mmol (391 mg) in the maximum daily dose	Not accepted. The guideline is clear that thresholds relate to anything equal to or greater than the value and the threshold of 17mmol

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ≥ 17 mmol (391 mg)	relates to the maximum daily dose so this information needs to be provided.
163 Parenteral (Less than 1 mmol per dose)	12	**Comment:** "Medicinal product" should be replaced by the shorter term "medicine". This brings the Excipients labelling in line with the QRD template, which uses the proposed term. The term "1 mmol" must be deleted as the unit "mmol" is not comprehensible for laymen. In addition, both texts relating to thresholds of 1 mmol and over do not provide amounts in mmol, which renders this unnecessary in the lowest category. Furthermore, the abbreviation "e.g." is not necessary and the space character between "sodium-" and "free" should be deleted. The first proposed change is almost 30 % shorter than the proposal dated 21 May 2015 (83 characters, including space characters, versus 114 characters). The alternative proposed change does not need the second sentence ("It is essentially 'sodium-free'.) and could be more demonstrative for patients (90 characters, including space characters). **Proposed change:** This medicine contains less than 23 mg per <dose>. It is essentially 'sodium-free'. Alternative proposed change:	First proposal accepted with minor editing revisions.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This medicine contains less than 1.1 % of the recommended maximum daily intake per <dose>.	
163 Oral / Parenteral (1 mmol [23 mg] per dose)	12	**Comment:** See previous line and under "1. General comments" for an explanation in relation to deleting information pertaining to table salt. The wording relating to the "dose" to the first sentence should be similar to the previous category. It makes no sense to fix it to "one dose" as contained in the original proposal. Using the suggested wording allows more flexibility and where the usual daily dose is, for example, three tablets, the MAH can also insert the daily dose. **Proposed change:** This medicine contains <X mg> sodium per <dose>. This is equivalent to <Y %> of an adult's recommended maximum daily intake of sodium.	Partly accepted with modifications.
163 Oral / Parenteral (17 mmol [391 mg] in the maximum daily dose)		**Comment:** See first line under "2. Specific comments on text" and under "1. General comments" for an explanation in relation to deleting information pertaining to table salt. Similar to the previous line, we do not recommend fixing the wording to the maximum dose ("The maximum recommended daily dose of this medicine contains <X mg> sodium.") For most medicines, the maximum daily dose would not be used. It must be decided, dependent of the medicine, which dose should be	Not accepted. The proposal has been updated to state how many doses a patient would need to take to reach the threshold. In addition to those on a low salt diet, people with other risk factors for cardiovascular risk might also be concerned about long term exposure to high levels of salt.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		provided; preferably the most commonly used dose, which could then be explained in the "comments" column of the Excipients guideline. The term "<or> <your child>" should be deleted as parents can comprehend that the word "you" refers to the patient. Where the patient has a caregiver (for example Alzheimer patients), the original version "...if <you> <or> <your child> need(s)..." would not apply. It is unrealistic for all package leaflets to cover all possible situations! The word 'doctor' should be included before 'pharmacist', similar to the QRD template. With 36 words, the last sentence of the original proposal is too long according to the readability guideline ("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.") It should be substantially compressed. The provided suggestion illustrates that this is possible without losing important information. **Proposed change:** This medicine contains <X mg> sodium per <dose>. This is equivalent to <Y %> of an adult's recommended maximum daily intake of sodium. Talk to your doctor <or pharmacist> if you need [product name] for a long time and require a low salt diet.	
163	13	**Comment:** This table may be subject to confusion. It does not clearly take	Partly accepted. Elements of this proposal have been incorporated with

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		into consideration that 1) the maximum daily dose of a medicine may depend on the indication and user group. 2) a medicine can be marketed in a range of medicinal products. Products may differ in their type of dosage form, strength, composition, other formulation characteristics, packaging, dosing device, user instruction). A certain medicinal product may be directed to the use by a specific patient population and also be linked to a certain maximum dose. 3) that single doses may be given different times a day; Therefore, the information in the package leaflet should be specific for a certain medicinal product (i.e. a medicine in a certain dosage form, with a particular strength, with other particular formulation characteristics such as taste and colour, with a particular formulation, packaging and user instruction) rather than the medicine as such. Moreover, sodium may be found in many substances. Therefore it may be clearer to state that sodium is the main component of table salt. **Proposed changes (in red):** - Column 3 change "Less than 1 mmol per dose" into "Less than1 mmol per single dose" - Column 3 change "1 mmol (23mg) per dose" into "1 mmol (23 mg) per single dose" - One single dose of this <unique reference to dosage form,	modifications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		strength, and formulation of the medicinal product> contains less than 1 mmol of sodium (23 mg), i.e. it is essentially 'sodium- free'. - One single dose <add the amount of the maximum single dose in SmPC, where relevant> of this <unique reference to dosage form, strength and formulation of the medicinal product> contains <x mg> sodium (main component of table salt). This is equivalent to <y%> of the recommended maximum daily intake of sodium for an adult. - One single dose <add the amount of the maximum single dose in SmPC, where relevant> of <unique reference to the dosage form, strength and formulation of the medicinal product> contains <X mg> sodium (main component of table salt). When taken <n> times daily, 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.	
163 Column "threshold"	13	**Comment:** To improve the readability, the value of the threshold should also be indicated within the third column of table 5. **Proposed change:** Thresholds should read as follows:	Not accepted. See reasoning above.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>- Less than 1 mmol per single dose

- ≥ 1 mmol (23 mg) per single dose

- Greater than 17 mmol (391 mg) in the maximum daily dose for adults.</td><td></td></tr>
<tr><td>163</td><td>13</td><td>Proposed change:
Red: proposal in new Q&A
Blue: proposal MEB

<table>
<tr><th>Name</th><th>Route of administra-tion</th><th>Threshold</th><th>Information for the Package Leaflet</th><th>Comments</th></tr>
<tr><td rowspan="2">Sodium</td><td>Parenteral</td><td>Less than 1 mmol per dose
Less than 1 mmol per single dose</td><td>This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e. essentially ‘sodium- free’.
One single dose of this <unique reference to dosage form, strength, and formulation of the medicinal product> contains less than 1 mmol of sodium (23 mg), i.e. it is essentially ‘sodium-free’.</td><td>1 mmol of sodium (Na) = 23 mg Na = 57 mg table salt (NaCl).</td></tr>
<tr><td>Oral
Parenteral</td><td>1 mmol (23 mg) per dose
≥ 1 mmol (23 mg) per single dose</td><td>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.
One single dose <add the amount of the maximum single dose in SmPC, where relevant> of this <unique reference to dosage form, strength and formulation of the medicinal product> contains <x mg> sodium (main component of table salt). This is equivalent to <y%> of the recommended</td><td></td></tr>
</table>
</td><td>Partly accepted – see comments above.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes					Outcome
					maximum daily intake of sodium for an adult.		
				17 mmol (391 mg) in the maximum daily dose Greater than 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. One single dose of <add the amount of the maximum single dose in SmPC, where relevant> of <unique reference to the dosage form, strength and, formulation of the medicinal product > contains <X mg> sodium (main component of table salt). When taken <n> times daily, 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.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
line 165 (below Table 5)	11	**Comment:** Instead of threshold, values could be explicit Current: Note: The threshold is a value, equal to or above which it is necessary to provide the information stated [1]. **Proposed change:** Note: The threshold is a value, equal to or above which it is necessary to provide the information stated [1].	Comment not understood. The expression and interpretation of thresholds apply throughout the Excipient Guideline and are explained in the excipients guideline.