GUIDE

On Information material and documentation

NB! You can search the in guidance by pressing "Ctrl + F" and entering your key word.

Index

1. General comments

The purpose of this guide is to summarize relevant information for pharmaceutical companies affiliated to ENLI for the purpose of preparing advertisements aimed at healthcare professionals in Denmark. The guide should be seen as a supplement to the guide to the Promotion Code and should also be read in conjunction with this.

If you want to know more about the rules that formed the basis for this guide, you can read more in ENLI's Promotion Code and the guide to the Promotion Code.

You can find the rules on ENLI's website: www.enli.dk/en

2. Scope

Note that, as a rule, the rules in this guide only apply to the pharmaceutical companies that have chosen to comply with ENLI's rules by affiliation to ENLI. ENLI is a self-regulation committee, set up by the pharmaceutical industry.

The rules of the guide govern only the contact between pharmaceutical companies (and third parties acting on their behalf) and healthcare professionals. The contact that is made directly with patients or with others who are not healthcare professionals, is not covered by this guide.

To see which companies have joined ENLI, you can find an updated list on the front page of www.enli.dk/en.

3. Definition of information material and documentation

Information material is the material that the pharmaceutical company typically prepares to promote sales, etc. (see the advertising definition below). In this context, where we are within the scope of the advertising rules, "information material" can thus also be referred to as advertising material. In this context, this does not refer to information material on health and illness or material included in an individual correspondence that is exempt from the advertising rules, cf. Art. 2, (2)(c).

Documentation refers to the sources on which the information in the advertisement is based. A medicines advertising must always be based on a scientific source. All statements about a medicine in a medicinal advertisement must be documented by reference to valid sources. This guide includes how various sources can be used (or not used) as a reference in a medicinal advertisement about the medicine's properties, including efficacy and safety.

4. Advertising rules

4.1. Definition of advertising

Advertising for medicines to humans means "any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products to humans". The definition of advertising is the same, regardless of whether you are solely subject to Danish law or also ENLI's rules.

It should be noted that this is a very broad concept of advertising, which means that most of the activities of pharmaceutical companies towards healthcare professionals will be regarded as advertising activities. This means, among other things, that companies should generally stick to what their medicine is approved for and nothing else, otherwise there is a risk that they will get into an illegal advertising situation.

4.2. Requirements for advertising in Denmark

Medicines that are not approved for the Danish market must not be advertised.

In Denmark, there are two requirements that must be met before a medicine can be advertised:

1. There must be an existing marketing authorization (valid in Denmark) and
2. The medicine in question must be price notified to the Danish Medicines Agency[1]

Furthermore, advertising of a medicine must be adequate and factual, and must not be misleading or exaggerate the properties of the medicine. Information in the advertisement must be in accordance with the approved product summary of the medicine, cf. Art. 4 (2) of the Promotion Code.

5. Information material

It is stated in Art. 7 (1) of the Promotion Code that medicinal advertising should encourage rational use of medicines by presenting medicines objectively and without exaggeration of their properties. Claims in a medicine advertisement should not imply that a medicine or active ingredient has special benefits, qualities or properties, unless proven. Such documentation should be quickly available through reasonable requests from healthcare professionals.

Thus, the advertisement must not exaggerate the properties of the medicine. Thus, the advertisement must contain, in all respects, correct, adequate and well-documented information that is not misleading by omission, ambiguity or the like.

All information contained in a medicine advertisement must be adequate, factual, accurate, current, verifiable and sufficiently detailed to enable the recipient to form a personal opinion on the medicinal value of the medicine, cf. the Promotion Code Art. 7 (3)

5.1. Therapeutic indication

The wording of the advertisement must not in any way indicate a broader indication than the approved indication described in the product summary.

This means, inter alia that an advertisement must not promote effects or other endpoints, including from legal sources compliant with Art. 7 in the Promotion Code, in a manner in which setup or general appearance can be (mis)understood as an expanded indication.

[1] Applies for pharmacy-only medicines.

- Information that is consistent with or complementary to the indication, and which is presented as information, can as a starting point be accepted in pharmaceutical advertising.

    - Data on the efficacy which is included in the summary of product characteristics 5.1, but which is not directly related to the indication, may be used informatively, but not be given a more or as prominent position in the advertisement as claims specifically related to the indication. This is e.g., the case for certain diabetes medicines that have secondary shown weight loss in patients in the study. It will be possible to mention results on weight loss in an informative way. See also the Guide to Promotion Code Art. 5 (1)(3).

    - The Appeal Board found in AN-2017-4715 that the setting of an advertisement, and in particular the use of the heading, where highlighting a word in the headline of the advertisement with a different color than the rest of the headline meant that it was used as a catcher. The Appeal Board thus states in its decision: "*The Board of Appeal, on the other hand, finds the actual setting of [xx] ad violating the Promotion Code. The use of the heading "[xx]", where the word "[xx]" highlighted in bold red color is the advertisement's central catch, implies a risk that the ad can be interpreted as an indication extension at an instant reading. Thus, the advertisement does not meet the requirements of the Promotion Code Art. 4 (2), according to which advertising of medicines must be adequate and objective and not misleading. As stated in the Guidance to the Promotion Code Art. 4 (2), it depends on a specific assessment of the form and content of an advertisement, to know if it is in breach of the requirement for objectivity.*"

It is the Investigator Panel's assessment that clinical endpoints are the subject of the assessment in Art. 4 (2) of the Promotion Code, whereas the medicine's cellular mechanisms of action cannot be considered to be subject to the same requirement of compliance in the advertisement. Thus, it is the Investigator Panel's assessment that cellular action mechanisms may be described in generalizing terms and that these mechanisms are not subject to a requirement that it be stated in the promotional part of the advertisement.

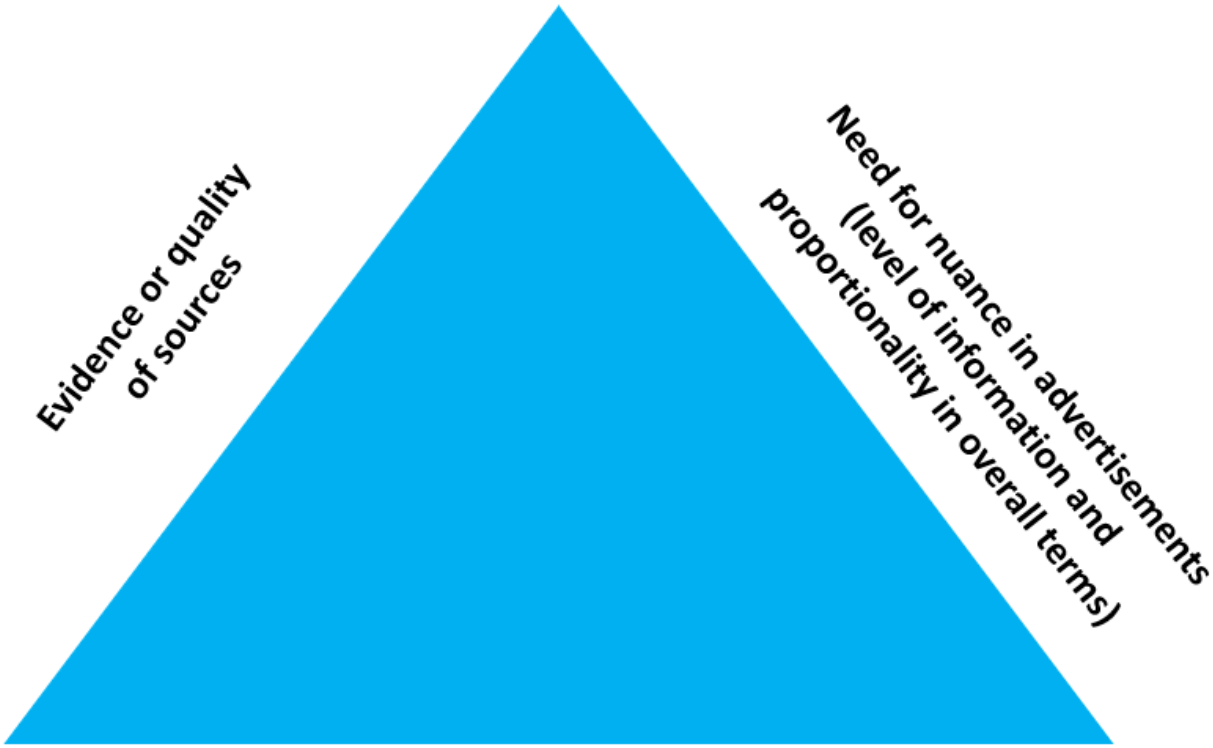
It is stated in the guide to Art. 7 (3) of the Promotion Code, that references must be loyal and references should be included to the extent necessary to illustrate the overall knowledge in the field. References must be clearly stated. None of these may refer to outdated information or otherwise be misleading.

If there are errata/erratum for a given publication, the corrected data which an advertisement refers to must be stated in the reference statement together with the article. Thus, in order for the advertisement to be regarded as adequate, both the article and its erratum must be stated.

5.2. Evidence hierarchy

As documentation of information about a medicine, in addition to the product summary, only scientifically substantiated studies that are peer-reviewed and published in established and independent Danish or foreign journal, professional journals, etc., may be used, cf. the Promotion Code Art. 7(5). Assessing when information in a medicinal advertisement is adequate and sufficiently detailed can be difficult. This guide is intended to provide some examples of cases in which information will be considered to be adequate, including the source's placement in the evidence hierarchy.

Basically, it can be said that the lower one is in the evidence hierarchy, the more information about the source must be included in the advertisement itself to ensure that the advertisement is adequate and not misleading.



At the top of the evidence hierarchy are the sources that typically have the highest degree of evidence or quality. This is where the large randomized clinical trials are located as well as meta-analyzes. At the bottom lies, among other things, case studies, expert opinions, etc. Although the above illustration of the evidence hierarchy and the relationship with the information-need might imply that if one is at the bottom of the hierarchy, such as with expert opinions, they can be used if you just elaborate information on the source. However, that is not the case. Under section 6 below, the sources that can be used in medicinal advertisements as documentation as well as the information-needs associated with the individual sources are reviewed. However, there are sources that will never be able to be used in medicinal advertising, e.g., expert opinions, posters, etc., cf. section 6.5.

6. Documentation

6.1 Documentation

As evidence of information about a medicine, in addition to the summary of product characteristics, only scientifically substantiated studies may be used, cf. Art. 7 (5) of the Promotion Code. The studies must have been published in recognized and independent Danish or foreign works, professional journals and the like. The studies must have been subject to an independent peer review prior to publication.

The fact that documentation (evidence) is included in the application for approval of a medicinal product is not in itself sufficient for it to be used as documentation for information about the medicinal product, cf. The Danish Medicines Agency's guidance for the advertising order, section 5.3.

Of the Danish Medicines Agency's guidance section 5.3. it states that the product summary is considered the basic documentation for the properties of a medicinal product. However, other documentation can be used if it meets the requirements for this.

Decision from the European Court of Justice

In Case C-249/09, the European Court of Justice has ruled on the scope of the provisions of the Medicines Directive on the use of information from medical journals or other scientific works and the scope of the provision that the information on a medicinal product must comply with the approved medicinal product SPC.

The case arose from a dispute between a pharmaceutical company and the Estonian pharmaceutical authorities. According to Estonian legislation in the area at that time, an advertisement for a medicinal product could contain only information that was also included in the approved summary of product characteristics.

According to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on establishing a community code on medicinal products for human use (Medicines Directive), Article 87 (2), "*All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics*". Furthermore, Article 91 (1) of the Medicines Directive states, that any advertisement for medicinal products directed at persons qualified to prescribe or supply medicines, inter alia, must contain the relevant information *which is compatible with the summary of the characteristics of the product*.

In the decision, the European Court of Justice ruled that, in addition to the approved product summary for the medicinal product, citations from medical journals or scientific works may also be used in advertisements for healthcare professionals. The European Court of Justice noted that, in recital 47 of the Medicines Directive, it is clear that medicine advertising which addresses healthcare professionals - although the advertisement contributes to informing them - is nevertheless subject to strict conditions and effective monitoring.

That being said, it is possible that information about the medicine, other than that stated in the medicine's SPC, may contribute to the healthcare professional's level of information, but that there are strict conditions for the use of such information.

The European Court of Justice states that, of course, a medicine advertisement must not make statements which are *inconsistent* with the information contained in the SPC of the medicine. It is stated in the judgment that "*[s]pecifically, no part of an advertisement for medicinal products may ever suggest, inter alia, therapeutic indications, pharmacological properties, or other characteristics that conflict with the summary of the product characteristics […]*"

> The European Court of Justice has interpreted the Medicines Directive as requiring that all statements contained in an advertisement for a medicinal product, which is addressed to healthcare professionals, be included in the SPC of the medicinal product or may be derived from it. The European Court of Justice notes that supplementary information in medical advertising for healthcare professionals must be consistent (compatible) with the SPC, thereby confirming or clarifying the information in the SPC, provided that this additional information meets the requirements that they should not be misleading, must promote rational use of the medicine by presenting the information objectively and without exaggerating the properties of the medicine. In addition, the information must be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form a personal opinion on the therapeutic value of the medicinal product concerned.

It should be noted that, as a rule, the SPC is always to be used as a reference. If the promotional material includes information about the medicine in question that does not appear in the SPC, scientific studies that meet the above criteria can be used. Such information must thus confirm or clarify the content of the SPC and thus be compatible with this, cf. the above on the European Court of Justice decision in C-249/09.

Randomized, controlled studies published in an established and independent journal and subject to an independent assessment are thus considered the primary supplementary source for the legal and approved summary of product characteristics.

For an explanation of how the terms “established”, “independent” and “independent assessment” are to be understood, refer to the guide to section 7 (5) of the Promotion Code.

For the types of statements (e.g., "best", "first", etc.) that are required documentation, please refer to the guidelines for art. 7 (1) of the Promotion Code.

In general, the published article used must be able to document the product advantage/claim highlighted in the promotional material. It is not acceptable to emphasize a positive opinion for the medicine in the article if the overall study is not able to document the statement. In principle, it is also not acceptable to emphasize a single study with positive mention of one’s medicinal product if this contradicts the overall knowledge in the field.

That a study is peer-reviewed and published in a journal that formally meets the documentation requirements in art. 7 (5) of the Promotion Code, does not mean that the reference can be used completely uncritically. For example, if the reference contains information on matters that contravene the SPC, the reference will in principle not be applicable even if it complies with art. 7 (5), as it is at the same time contrary to other provisions of the advertising rules. See also the Appeals Board's decision in AN-2017-1490.

It is the responsibility of the pharmaceutical company to document that material meets the documentation requirements.

ENLI does also refer to the above regarding the decision of the European Court of Justice, according to which information derived from scientific articles, etc. must confirm or clarify information in the medicine's SPC. Thus, no information can be provided in a medicine advertisement which does not have a direct link with the information in the approved SPC.

6.2. Documentation on factual information in the advertisement

The European Court of Justice has stated in C-316/09 that the definition of advertising is broad, whereby material containing only objective information can be considered advertising if the message is intended to promote the prescription, supply, sale or consumption of medicines. It is the opinion of the Investigator Panel that information on the properties of the medicines, including efficacy and safety profile, should be made solely with reference to approved SPC or scientific studies. Purely objective/factual information, provided that they are accurate, thus not showing anything about the properties of the medicine, but which only states factual information, can be included in an advertisement with reference to sources other than SPC and/or scientific studies.

Accordingly, factual information must be kept completely objective and neutral, and thus should not appear in the advertisement in a way that it can be construed as laudatory for the medicine in question. It can e.g., be information about the price of the medicine or that one's medicine has obtained a given reimbursement status after a decision with the Danish Medicines Agency.

6.2.1. Examples of sources, which apply as reference for factual information

Sources that do not meet the documentation requirement in Art. 7 (5) of the Promotion Code, must not be used to document the properties of the medicine, including efficacy and safety profile. Thus, the following examples of sources can only be used to provide factual information relating to the medicine.

- **Guidelines from medical societies (both Danish and foreign)**
    - It is stated in point 5.3. in the Danish Medicines Agency's guidance for the advertising order, that
        - *"Guidelines from medical societies cannot be used as independent documentation and reference for information about a medicinal product's properties, including safety and efficacy, in a medicinal advertisement. The one responsible for the advertisement may insert a supplementary reference to a guideline if it contains a reference to a scientifically supported study that has been published and meets the conditions for documentation. If necessary, there must also be a reference to the article itself, and it is a prerequisite that the guideline does not contain information about the medicine that is inconsistent with the product summary."*
    - Information from guidelines can be used as documentation for factual information about e.g., diagnosis or diseases.
    - As an example of factual information, mention may be made of the fact that a guideline exists in the field and that your medicine is included in the guideline. This is, of course, provided that the information on the medicine in the guideline is in accordance with the applicable SPC.
    - Factual information must be kept completely objective and neutral and should not appear in the advertisement in a way that can be perceived as laudatory for the medicine in question or as the primary intention of the material.
    - No direct or indirect comparison with other medicines must be made on the basis of a guideline.
    - An advertisement for a medicine cannot be based solely on references to guidelines.

- It is noted that if information materials on health/disease do not - either directly or indirectly - contain information about medicines, a reference directly to the guidelines can be made, provided that these do not contain any mention of the effective use of the medicinal product contrary to the medicine's SPC.
- A guideline can be provided in its entirety to healthcare professionals if the guideline is in accordance with the SPC of the medicine, and the distribution is neutral and thus without laudatory remarks about the medicine in connection with the delivery of the guideline. If the distribution is unsolicited, a compulsory text must also be provided for the medicine at the same time as the distribution of the guideline.
- For examples of use of guidelines, see section 9 on FAQ and Appendix A.

- **Danish Medicines Council (Medicines Council)**
  - The Medicines Council's recommendation is based not only on scientific studies and their weighting - but also on the economics of the use of the medicine.
  - A recommendation from the Medicines Council cannot be used to address a medicine's properties, including to conclude that the medicine is better than other medicines. Therefore, no direct or indirect comparisons should be made with competing medicines on the basis of the recommendation of the Medicines Council.
  - The Medicines Council's recommendation must not be the primary intention/sole message in an advertising. Therefore, it will not be possible to apply the recommendation of the Medicines Council in the heading of an advertisement, as information from the Medicines Council must not be the primary or essential element of the advertisement.
  - Information from the Medicines Council can thus be used as a reference for factual information in the advertisement, when the information is not used to describe something about the properties of the medicine or to compare the medicine - directly or indirectly - with other medicines.
  - It is considered as a claim of the medicine to write that one's medicine is recommended by the Medicines Council as the *first choice*, as there is implicitly a comparison with other medicines.
  - It is possible to inform about a given recommendation from the Medicines Council or similar, in an informative and non-laudatory way. This could, e.g., be as a sub-item of an advertisement which highlights other scientific information about the medicine.
  - If information from the Medicines Council is used as the primary basis for an advertisement, it may contravene Art. 7(5) of the Promotion Code, since this is considered a claim - especially if the primary message concerns e.g., an assessment and the placement of the medicine, where the source is used in a laudatory way in the material, cf. R-2017-3397. A similar decision was made in R-2017-2646, where the advertisement's statements regarding first choice with reference to RADS had a prominent place as the primary and sole statement of the advertisement, which was further strengthened by the overall visual and laudatory expression of the advertisement. For other decisions on the use of information about the Medicines Council in pharmaceutical advertisements, see e.g., R-2021-0244, R-2021-1099 or R-2021-4216.

- Medicines advertising may contain objective and factual information that a particular medicine has been recommended by the Medicines Council as a possible standard treatment for a specific therapeutic indication. However, in order for a promotional material for a medicine to be considered adequate, it will require that the entire recommendation, including the concerns and reservations are included in the promotional material. Thus, it will not suffice to say "Recommended as standard treatment" alone. See example in Appendix A.
- The recommendation of the Medicines Council can be given in its entirety to healthcare professionals, if the recommendation is in accordance with the SPC of the medicine. The distribution must be done in a neutral manner, and thus without any laudatory remarks about the medicine in connection with the distribution. If the distribution takes place unsolicited, a compulsory text for the medicine must also be provided.

- **IRF, RADS, KRIS**
  - Information from, e.g., IRF (Rational Pharmacotherapy Initiatives), former **RADS** (Council for the Use of Expensive Hospital Medicine) and **KRIS** (Coordination Council for the Use of Surgical Medicine) can be used as reference for factual information in the advertisement when information are not laudatory of the medicine by describing anything about the medicine's properties or for comparing the medicine - directly or indirectly - with other medicines. See also above regarding the Danish Medicines Council.

- **Medicin.dk, Sundhed.dk or the like.**
  - Web sites containing professional information on illness and health can be used as a reference for factual information about e.g., symptoms of illness and the like. Please note, however, that in the case of common knowledge, which can also be found in textbooks and which must be regarded as well-known by professionals, no documentation is required for this in the promotional material. When asked by ENLI whether something is common knowledge, it should be documentable through reference to textbooks.

6.3. Sources, which apply as documentation in an advertisement for medicines

In ENLI's opinion, the following can be used as documentation for information on the medicine's properties, including efficacy and safety profile:

- The approved product summary (**SPC**)

- **Scientific studies**, published in established and independent Danish or foreign magazines, journals and the like, and which have been subject to an independent assessment prior to publication. Please note that simply because a study is peer-reviewed and published in a journal that formally meets the documentation requirements of Art. 7(5) of the Promotion

Code, it does not mean that the reference can be used completely uncritically. Here, consideration must be given to where in the evidence hierarchy the study in question lies and whether there may be a need for more detailed information in the medicine's advertising to ensure that the information is adequate, factual, accurate, up-to-date, verifiable and sufficiently detailed for the recipient to form a personal opinion on the medicinal value of the medicine, cf. Art. 7(3) of the Promotion Code.

- **Systematic overview articles with meta-analysis**, i.e. a total statistical processing of data from several medicine's tests, if there is full scientific coverage for the statements made and if the study is published in a scientific journal with independent review (peer review). However, scientific studies in such review articles may only be referred to if they each meet the requirements for documentation.

6.4. Other sources which apply as documentation in an advertisement for medicines

Common to the sources mentioned in Section 6.4. is that these are typically sources that are further down the evidence hierarchy and where additional information is needed in the advertising to ensure that the information is adequate, factual, accurate, up-to-date, verifiable and sufficiently detailed for the recipient to form a personal opinion on the medicinal value of the medicine, cf. Art. 7 (3) of the Promotion Code and Section 7.1.

- **Registry studies, observational studies, cohort studies, real world evidence/data and the like:** Data from such studies should be used with caution, since there may be uncertainties in such studies, including off-label use. The fact that a study is published in a journal, which formally comply with the Promotion Code's Art. 7 (5), is therefore not a guarantee that scientific weaknesses in the study have been taken into account. It can in advertising contexts e.g., cause unauthorized use, risk of off-label option and some methodological issues related to e.g., control groups, applied statistics, etc. See also AN-2017-1490, in which it inter alia is highlighted that

    - *"when Real World Data (RWD) is presented in promotional materials, this must predominantly be set in a context with data from randomized clinical trials (RCT). In relation to an RCT study, it is as mentioned not a requirement for an observational study to have a control group and the inclusion can disagree with the medicinal product's authorized conditions. One should therefore base its claims in a drug advertisement on its approved SPC and possibly RCT-studies (meeting the documentation requirements), and only use observational studies as information, and only if this is not contrary to the SPC. This means that the source material as the SPC and RCT studies, should be used as a primary reference in advertising material, while observational studies/RWD does not have the same evidence-base and therefore should only be used as a supplementary information".*

- **Non-clinical studies**: Non-clinical studies, e.g., be a pharmacodynamic study, which is a study (possibly hypothesis generating) in which a small group of people (can be both healthy subjects and patients) is investigated for mechanisms of action (dynamics), e.g., at the receptor level. Such studies cannot be compared with the large clinical RCT studies. In AN-2018-0747, the Appeals Board stated that

- "*The Board of Appeal may agree that pharmacodynamic studies can, in general, be used as documentation for information on a medicine, to the extent that the conditions in art. 7 (5) of the Promotion Code is fulfilled. Thus, only scientifically substantiated studies that have been published in independent and established Danish or foreign works, professional journals and the like, and which have been subject to an independent assessment prior to publication, may be used.*

  ...

  there is still a risk that, after the adjustment of the Advertising, relevant readers based on the results of the reference may perceive that [medicine X] is overall [medicine Y] superior - regardless that these results, according to the reference, must be seen with reservation. In particular, the Board of Appeal emphasizes that, among general practitioners and other readers in the target audience, there is hardly any knowledge - or sufficient knowledge - about the nature and content of pharmacodynamic studies in order to understand and assess the meaning of the reference. The advertisement should therefore have included additional information about the data base and the content of the study in order to ensure the readers' understanding of the basis for the statements in the Advertising."

Thus, the promotional material must contain information about the data basis and the content/design of the study, in order to ensure that the readers of the advertisement can relate statements in the advertisement to the data on which they are based.

- **Post hoc analyzes:** In a scientific study, a post hoc analysis (from Latin post hoc, "after this") consists of statistical analyzes that were not specified before the study was started, e.g., a large randomized and controlled trial that is the basis of the medicine's approval. Post hoc analyzes have some statistical reservations but can be used in advertisements if the results of this are put in the context of the approved therapeutic indication and if an adequate level of information is included in the advertising.

6.5. Sources which do **not** apply as documentation in an advertisement for medicines

In ENLI's opinion, the following cannot, as a rule, be used as documentation for information on the properties of the medicine, including efficacy and safety profile:

- **Expert opinions and the like**: Even if such a publication is published after peer review and in a recognized scientific journal, it will still be the writer's position, which is not necessarily in accordance with the general opinion for the disease area/medicine. This type of publication is not legal as a source in a pharmaceutical advertising.

- **Casuistics:** (public description of an individual case of disease) cannot be used as documentation. Casuistics describe a single-person effect, and on that basis, they cannot be used to document the effect that clinical studies based on population-level efficacy measures can document. An individual-level claim is therefore not in accordance with general principles of evidence-based medicine, and since claims must be documented by legal references, cf. Art. 7 of the Promotion Code, the documentation requirement for such a claim is not complied with.

- **Abstracts and posters**: These cannot be equated with scientific articles, partly because various details of the study are often missing in abstracts and posters, and partly because abstracts and posters are generally not subject to the same strict review of the scientific value of the publication as articles in scientific journals. This fundamentally applies irrespective of whether the abstract or posters have been published and peer reviewed. If abstracts are involved relating to a scientifically supported investigation that is being published in a recognized, independent scientific journal which has been subjected to peer-review prior to publication, this can however be regarded as documentation. From the guidelines for the advertising order, section 5.3. it states that it is not sufficient "*that a study has been subjected to an impartial evaluation prior to an oral presentation at a congress or a symposium, and publication in abstract books published by a congress organizer, or publication on a professional association's website cannot be equated with publication in recognized and independent professional journals, etc."*

- **Data on file**: Such data cannot be used since they do not satisfy the requirements of Art. 7 (5) of the Promotion Code. Thus, data on file is not published information, nor is it peer reviewed.

- Information about an ongoing **clinical trial** that has been published, for example on www.clinicaltrials.gov cannot be used, since such information does not comply with the requirements for documentation, cf. Art. 7(5) of the Promotion Code.

- **Foreign recommendations** are not acceptable as references since these are individual countries' recommendations for the use of specific medicinal products and there may be reasons why these are not applicable in Denmark. For example, recommendations are not accepted from FDA (Food and Drug Administration, (USA)) or NICE (National Institute for Health and Clinical Excellence (UK)). In the same way, neither are recommendations from WHO immediately acceptable since recommendations from them may be based on general societal or political considerations, which could mean deviating from the approved product summary.

- **Health economic analyses/cost analyses** can contain both factual information and (possibly indirect) claims about the effect of the medicine. However, health economic analyses are not "factual" in the sense that they are primarily based on (subjective) assumptions about the future. Health economic analyses are used in market access contexts, e.g. for applications for general reimbursement or general conditional reimbursement with the Danish Medicines Agency. It thereby becomes a submission from the pharmaceutical company and is included in the application along with a wide range of other information. Thus, you can only make "raw" and simple price comparisons based on prices and DDD (defined daily dose). You cannot make comparisons based on different assumptions (e.g. about hospitalization, side effects, etc.).

- **EPAR** (European Public Assessment Reports) are not suitable as documentation for pharmaceutical advertisements. Studies in this connection are weighted in EMA's assessment, after which the result is evidenced by the SPC with the weight as EMA chooses it must have, and on an aggregate basis of all available evidence, the therapeutic indication of the medicinal product is given.

    - EPAR is an underlying document, which can include more information than is included in the SPC. Thus, one cannot choose to highlight something from EPAR

in a pharmaceutical advertisement, which is not recognized by the therapeutic indication in the SPC, since it will be considered off-label advertising.
- If a company wish to use EPAR laudatory in their pharmaceutical advertisements, one must therefore wait until the desired data is recorded in the SPC of the medicinal product.

- **PSUR** (Product Safety Update Report) is the pharmaceutical company's own presentation of safety data in connection with an application for marketing authorization for the medicine. It is thus the pharmaceutical company's party submissions to the process of the pharmaceutical authorities and therefore not suitable as documentation for medicine's advertising.

- **Decisions from courts of justice**: The use of a decision from either a Danish or foreign court of justice will not be in accordance with Art. 7 (5) of the Promotion Code, on documentation. If you want to make claims of the properties of your medicine, you must refer to the approved SPC or scientific studies.

- **Market research:** The information obtained from a market study cannot in itself constitute a basis for a claim about a medicine.

7. Adequate Advertising

7.1. Adequate Advertising

Sec. 63 of the Medicines Act contains certain fundamental requirements for the content and format of medicinal product advertising, cf. the guidance to the Advertising Order on Sec. 3.1, which states that: *"Firstly, advertising must be adequate. For instance, an advertisement must contain adequate information so that recipients can understand and assess when and under which circumstances the medicine can and should be used and when not to use it. By contrast, an advertisement is not adequate if it uses such broad terms that it is likely to promote the consumption of a medicine when in fact it is not particularly suitable to use under the given circumstances. The provisions detailing an advertisement must contain a number of compulsory details; see sections 4.5 and 5.1, are based on the requirement for medicines advertising to be adequate.*

Secondly, advertising must be factual. Therefore, medicinal products must not be marketed in the same aggressive and consumption-encouraging manner as general consumer goods. Advertisements for medicinal products must not be designed to or likely to generate unnecessary increases in the consumption of medicines. The advertisement must furthermore be based on professional and relevant information about the medicinal product. Whether an advertisement fails to be factual is determined by assessing the form and content in each specific case.

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Thirdly, advertising must not mislead or exaggerate the properties of a medicinal product. This means that the form and content of an advertising must not lead medicine users and persons prescribing or dispensing medicinal products to form misconceptions about the medicinal product, including its effects, adverse reactions, price, ingredients, etc., disease or treatment. Nor must an advertisement put a medicinal product in a more favourable position than other corresponding and perhaps even more suitable medicinal products. An advertisement for a medicinal product must neither in form nor content mislead or be designed to

mislead the persons it is aimed at or exaggerate the properties of the medicine. It depends on an overall assessment of the advertisement, including text, images, illustrations, etc., whether the advertisement is misleading or exaggerates the properties of the medicine.

Fourthly, the information contained in the advertisement must comply with the approved summary of product characteristics (SPC). The particulars in the SPC include information about the composition of the product, pharmaceutical form, therapeutic indications (applications), contraindications, adverse reactions, precautions for use, dosage and warnings, if any. This means that the content of the advertisement must not be inconsistent with the particulars of the SPC. It is possible to deviate from the wordings of the SPC to the extent that the requirement for factual information is met. An advertisement for a medicine may include statements that supplements the information in the SPC, provided they confirm or specify information in the SPC, and the information otherwise complies with the SPC. These may be, for example, documented statements about the effect or side effects of the medicinal product that confirm or clarify information in the summary of product characteristics and are compatible with the summary of product characteristics. The information in the advertisement must not be misleading or exaggerate the properties of the medicinal product. An advertisement for a medicine must only include information about authorised indications as appearing from the authorised SPC."

Advertising for a medicine that is sent or distributed to healthcare professionals for promotional purposes must contain, as a minimum, the so-called compulsory information, which is stated in Art. 5 of the Promotion Code. This information helps to make the advertisement adequate and must therefore, as a starting point, be an integral part of the advertisement, cf., Art. 5 (2) of the Promotion Code and the guidance to this. Compulsory information is not dealt with in detail in this guide, so please refer to the Guide for the Promotion Code for further information on this.

The assessment of whether commercial, generalizing statements are sufficiently adequate and objective are generally complex. There will often be a need to substantiate commercial statements with scientific statements/data that, directly in the advertising context, adequately nuance the information level. Although this can be difficult in situations where the scope of the advertisement is a banner commercial. However, it is the Investigator Panel's assessment that an advertisement should generally have an adequate level of information that is independent of the advertising format and scope. In AN-2018-0346, the Appeals Board also stated that "*Notwithstanding the special nature of roll-up as advertising medium, the information must not be so brief that it may seem misleading*."

This means, among other things, that brief statements such as "Up to 4 years of effect", "Medicine X reduces the attack rate" or "significantly lower mortality" must be elaborated with quantification of data, so that the recipient of the advertisement receives an objective data basis which supports the statement. This data elaboration of the commercial statement can e.g., be done in direct relation to the statement or by means of a footnote in which study information can also be stated.

Data in the advertisement of a relative risk reduction of X% should be put in the context of the absolute risk. One can, for example have shown that the relative risk of mortality is reduced by 100%, but if the absolute risk is thereby only improved from 0.00002 to 0.00001, it can be misleading to state the relative risk alone.

In some cases, there may be a need to include certain reservations in the advertisement, including the article authors' reservations in the advertisement to avoid the risk of the reader misunderstanding the medicine, especially if the article states that the study results include a reservation.

The advertisement must, in its overall design, be adequate, regardless of the context in which it is presented, as well as in relation to the target group, cf. AN-2018-0346 where the Appeals Board, among others found it unimportant that "*the healthcare professionals present may have special expertise in the area, and the access to obtaining in-depth information, including through company representatives at the booth, is of no importance.*"

Thus, in its design, a pharmaceutical advertisement must contain sufficient information for the recipients of the advertisement to understand the context and thus understand and assess the data basis on which the statements in the advertisement are based.

7.2. Endpoints and study design

In an advertisement where claims are made with reference directly to the **primary endpoints** of the phase 3 study that underlies the approved therapeutic indication, there is no immediate need for additional information on study design, etc. in order for the advertisement to be considered adequate. Here, a reference to SPC and/or the underlying publication will suffice, although information about study design also contributes to the information base.

It is the opinion of the Investigator's Panel that there is the possibility of differentiation of e.g., **secondary or tertiary endpoints**, however, always taking into account the medicine's therapeutic indication range and the approved SPC for the medicine, as well as the requirements for adequate and objective advertising. This will often mean that a brief statement of the study, its endpoints and the result thereof (a brief study description) is implemented in order for the advertisement to be considered adequate, cf. Art. 4 (2) of the Promotion Code. This means, inter alia, that only clinically recognized endpoints may be used for the area of therapy that confirms or clarifies the SPC. It is considered essential that the listed study description also provide data for the outcome of the other step-higher endpoints (e.g., the primary endpoint of the study if the secondary endpoint is used as the differentiating element) so that a contextual understanding of the presented endpoint is met, cf. R-2024-0465.

Randomized controlled trials - so-called RCT studies - are considered the primary supporting source material for the legal and approved SPC (see section 6 above).

However, it is the opinion of the Investigator Panel that Art. 7 of the Promotion Code also allows for the use of other types of studies, if it is ensured that the information level in the advertisement meets the requirement that the advertisement as a whole must be adequate.

Observational studies, register studies and the like (including real world data [RWD]) can e.g., be used in advertising context. If such studies are used as a basis for claims in advertising, the claims must be in proportion to the data/evidence hierarchy, which is why in the promotional part of the advertising, more detailed study information must be included such as, e.g., the data basis, the purpose of the study, results and important reservations in the study, cf. AN-2018-0747 and AN-2017-1490 as well as section 6.4. above.

Although studies are designed as an RCT study, however, there may still be a need to increase the level of information in the advertisement for it to be considered adequate. For example, there could be non-clinical RCT studies, such as pharmacodynamic or pharmacokinetic studies. Such studies can be used as a basis for differentiation in an advertisement - however, the advertisement must have sufficient study information and data, including significant reservations, to ensure the recipient's understanding of the basis for the statements in the advertisement, cf. AN-2018-0747.

Randomized controlled clinical trials can assume several different study designs. Many RCT studies are designed as a **non-inferiority** study, which means that the study is designed to demonstrate that the active arm of the trial is "no-worse" than the comparator (placebo or competing medicien). In addition to demonstrating non-inferiority, (secondary) valid and factual conclusions about e.g., superiority depending on the statistical analysis plan can be made. It is ENLI's assessment that non-inferiority RCT studies can be used as a differentiating element of an advertisement, provided that there is a sufficient level of information in the promotional part of the advertisement. See also AN-2019-0926.

The Investigator Panel notes that nuanced information (such as study design, etc.) that is necessary for an advertisement to be considered adequate must be placed in the "promotional part" of a material. In a material that has a continuous shape, such as a multi-page leave-behind or a slide show, there is a greater degree of flexibility in that information can be presented in a continuous fashion during the material.

8. Comparative Advertising

8.1. Comparative Advertising

Comparative advertising is advertising that directly or indirectly refers to another medicinal product. However, it will always depend on a specific assessment, where the content of the advertisement is evaluated in each case.

In principle, comparative advertising will be legal when the advertising as a whole is adequate, correct, relevant and loyal. The comparison must also be objective and relate to documentable information.

Comparative advertising must, as a starting point, be drawn up on the basis of the information in the product summaries of the medicinal products included in the comparison. Thus, documentation of the comparative medicines can be obtained by reference to their SPCs. For those medicinal products in which the SPC does not contain information on the conditions covered by the comparison, the comparison may be based on scientific studies, e.g., a head-to-head study.

It should be noted that comparative advertising, which is based solely on product summaries, will not always be adequate and factual, cf. Art. 4 (2) of the Promotion Code and AN-2012-2713.

It shall clearly appear of a pharmaceutical advertising that contains a comparison between multiple medicinal products, what medicines the comparison includes. The comparison must be limited to medicinal products, which it is objectively appropriate to compare, e.g., medicines with coincident scope, cf. the Promotion Code Art. 8(1). There is also an obligation to present the compulsory text for the company's own medicine. See also AN-2018-3964, which states: "*an unfair comparison of medicinal products has been made in violation of Section 8 (1) of the Promotion Code. This slide compares the efficacy and safety endpoints of [X] and [Y], regardless that [...] medicine [X] is not approved for the therapeutic indication, thus, it is an off-label comparison contrary to the advertising rules.*"

In principle, the same rules apply to documentation for comparative advertising as to ordinary advertising. The documentation basis must meet the requirements of Art. 7 (5) of the Promotion Code. The Appeals Board has in AN-2017-1564 also stated "*The overall requirements of factual and adequate advertising has central importance in relation to comparative advertising, in particular because this form of advertising is an essential differentiation and positioning tool [...]. Regardless of accordance with other*

rules of the Promotion Code, advertising of medicinal products must comply with the Promotion Code Art. 4(2)... "

The direct comparison is made in a head-to-head study where the study of medicines is done under the same conditions. However, even in these cases, there may be a need to supplement the comparative advertisement with additional information so that the advertisement is adequate and factual - and not least loyal to the competitor's medicine with which one compares.

This may be the case if a pharmacodynamic study is used as the basis for its comparison. The Appeals Board found in AN-2018-0747, that the Appeals Board acknowledged that the pharmacodynamic study in the case complied with the requirements for documentation in Art. 7 (5) of the Promotion Code, but considered that:

> *"there is still a risk that, after the adjustment of the Advertising, relevant readers based on the results of the reference may perceive that [medicine X] is overall [medicine Y] superior - regardless that these results, according to the reference, must be seen with reservation. In particular, the Board of Appeal emphasizes that, among general practitioners and other readers in the target audience, there is hardly any knowledge - or sufficient knowledge - about the nature and content of pharmacodynamic studies in order to understand and assess the meaning of the reference. The advertisement should therefore have included additional information about the data base and the content of the study in order to ensure the readers' understanding of the basis for the statements in the Advertising."*

This was also the case in a case concerning comparison based on a Real World Data study in AN-2017-1490, where it was emphasized, among other things, that:

> *"[Pharmaceutical company X] in the doctor letter refers to a Real Life Evidence (RLE)/ Real World Data (RWD) study published in JAMA Internal Medicine. This is a study that has been peer-reviewed and published in a recognized and independent journal, and so the documentation requirements in Art. 7(5) of the Promotion Code is formally fulfilled. However, this does not mean that such a reference can be used uncritically and without reservation.*
>
> *The article in JAMA Internal Medicine contains significant reservations on the part of the authors. [Pharmaceutical company X]'s use of the study as a reference in the doctor letter without information about the reservations is misleading and disloyal in contravention of the provisions of Art. 7 (3) of the Promotion Code and Art. 8 (1). [Pharmaceutical company Y] has also highlighted in its complaint various scientific weaknesses in the study, which should have given rise to special caution, not least in relation to reference in an advertising context.*
>
> *RLE studies should generally be used with caution, as these studies may be subject to uncertainty."*
>
> For further, please see section 6.4. regarding the use of RWD-studies.

In connection with references to relevant studies, it is noted that one must not single out one single study indicating positive results for the company's medicine, if it will appear misleading in relation to the overall knowledge in the field (so-called cherry picking). One must specify an exhaustive list of resent/relevant references, published in recognized journals, cf. the guide to Art. 8 (1) of the Promotion Code.

Documentation of "absence" of parameters with the comparative medicinal products should be presented to ENLI upon request. This can be e.g., SPC's or studies. This will, among other things, be relevant

for claims of, for example, being the "only one" on the market in an area. Read more in the Guide to Sections 7(1) and 8(1) of the Promotion Code.

8.2. Price comparison

If a specific comparison is involved, for example the prices of pharmacy-only medicinal products, a comparison can be made on the basis of the prices published on www.medicinpriser.dk. In price comparisons, the current price must be given. An advertisement that contains a price comparison is only adequate, cf. Section 63 of the Medicines Act, if it contains information about the current prices that are included in the price comparison, cf. section 5.1.8) in the Danish Medicines Agency's guidance for the advertising order.

Price must only be disclosed by comparative advertising if price statements are made in the advertisement. Prices must be up-to-date and correct in price comparisons, at the time the promotional material is used.

A price-comparing advertisement for medicines must contain all medicines with the same indication. One cannot therefore choose to compare only on price with one selected competitor. It follows from the guide for the Advertising Order, cf. 3.2 that a comparison is basically adequate only if it includes all synonymous (as well as any parallel imported) medicines that do not differ in either pharmaceutical form or strength or differ significantly in package size. However, pharmaceuticals with a negligible market share (2-3%) may be omitted from the comparison. It is ENLI's assessment that by synonymous medicinal products is meant medicinal products with the same area of use, active ingredient, medicines strength and form.

If the intention of the comparative advertising is to compare itself with a competitor on parameters other than price, e.g., efficacy and the adverse reaction profile, the price can be included as a further point of comparison without the obligation to include all relevant medicines in the comparison. If, on the other hand, the intention of the medicine's advertising is to compare itself to the price, all relevant medicines must be included in the comparison, cf. above.

For price comparisons, the calculation system employed and the basis for this must be precisely stated, i.e. the daily dosage used for calculations and tablet size, pack size and pack price. Generic and trade names and also information about pack sizes and prices, dosage for the products compared, etc., must be stated if such information differs from the information about the company's own medicine. Price comparisons in which analogue or synonymous products are included must only be based on the dosage approved by the Danish Medicines Agency. Accordingly, treatment prices where there is an approved dosage range must be stated for the highest and lowest approved daily dose for a 24-hour period.

- If all prices have not been calculated, they must be based on relevant, common pack sizes, which give the lowest price for the competitor.

- For certain medicines, it may not be possible to give a predetermined daily dose, for example certain medicines used for headaches. In such situations, price comparisons may be based on a comparison of prices for the recommended starting dose and for the dosing range from the smallest start dose to the highest recommended dose. A price comparison

may accordingly not be based here on how frequently certain doses are used for treatment.

In an advertising with price comparison sent to hospital clinics/hospitals, tender prices which pharmaceutical companies are obliged to use when selling medicines to the hospitals, can be used.

9. Q & A

Scientific studies that confirm or clarify information in the SPC

1. A study is mentioned in the SPC, but the specific endpoint (e.g., time to disease progression) was not reached for the medicine when the SPC was updated. We have now conducted a study that shows results for the endpoints we have not been able to prove previously. May we use the new data in advertising?

   Answer: *No. If new results are found for endpoints that were not included in the SPC upon approval of the medicine, you should contact the Medicines Agency to update the SPC of the medicine. Using studies that now show results that could not previously be shown is incompatible with the current SPC. See section 6.1. above, regarding EU-decision C-249/09.*

2. We have done a new study after the approval of our medicine which has indication for the treatment of COPD (the new study is in accordance with approved indication, correct dose and patient population, etc.). In the new study, it has been shown in a secondary endpoint that the cases of exacerbation requiring hospitalization are 26%. May we use this new secondary endpoint in advertising, even if there is no mention of hospitalization requiring exacerbation in the SPC?

   Answer:
   Yes, as the new study in this case is considered to be compatible with SPCs, thereby clarifying or confirming the information in the SPC. The medicine has the indication 'treatment of COPD', and the broad indication means treatment of all clinical aspects of COPD. For example, exacerbation requiring hospitalization is considered a clinically relevant, recognized and validated endpoint for the disease. In addition, there must be adequate information about the study, its endpoints (especially the primary endpoint) and results, so that the secondary endpoint used is presented in the context of a study design and especially the primary endpoint and its results.

3. Can information about improved quality of life be used in an advertisement?

   Answer: *No, not just. As stated in EU decision 249/09, in addition to information provided by SPC, only information from scientific studies which confirm or clarify the information contained in SPC may be used. Although quality of life may be relevant, it is, as a starting point, too far away from the medicine's indication for it to be said to confirm or clarify the information in the SPC.*

4. We have now published data on a follow-up study/continuation study/extension study (a continuation of the RCT study that is the basis for the approval) that meets the documentation requirements in the Promotion Code. This follow-up study shows efficacy data after 3 years of treatment. Can efficacy data from the follow-up study (3-year data) vs. 1-year SPC data, be used in advertising?

Answer:

It can be difficult to assess a follow-up study compared to the registration study as the design typically changes - blinding is removed, patients may be allowed to cross over to the new medicine, statistical methodology changes, etc. Efficacy (and safety) estimates are difficult to compare directly to the registration study.

However, it may be possible to use the results, and in certain situations it must be ensured that data from the follow-up study is put into context with data from the registration study so that it is not mentioned in a laudatory fashion and exaggerated. Special attention should be paid if data from the follow-up study shows better results than what has been demonstrated in the registration study, as this may be considered to be in conflict with the efficacy and safety data reported in the SPC. In such cases, you will have to update the SPC of the medicine in order to use the follow-up study as a reference for your claim.

For example, it cannot be said to confirm or clarify the information in an SPC if you could not show significance for a specific endpoint in your registration study, e.g. OS (overall survival), but show significance in the follow-up study with effect data of 3 years. In this case, the SPC will need to be updated.

Conversely, it may be possible to use the follow-up study if, for example, the SPC states that OS is seen at 14 months, where a follow-up study after 3 years confirms this by showing OS at 14 months. The follow-up study is seen as a supplement to the SPC, which confirms the information in the SPC.

An example of clarifying information in the SPC could be that the SPC states in the dose section that the medicine should be taken 1-2 times a day. In a follow-up study, it can be documented (and clarified) that 82% of patients in clinical practice only need to take the medicine once a day. Here, the follow-up study has clarified the content of the SPC.

5. Many companies would like to unsolicited distribute collections of abstracts with reference to the full articles. So, e.g., the doctor for a visit by a sales consultant can ask to have these collections of abstracts pertaining to a particular medicine or disease area. May such abstract collections be distributed unsolicited as promotional material?

Answer: *Yes. These are abstracts for peer-reviewed and published articles that comply with the documentation requirements in Art. 7 of the Promotion Code. This is, of course, provided that the studies in question comply with the rules of the Promotion Code itself.*

6. In continuation of the foregoing questions about abstract collections: May such abstract collections be distributed if the collection does not concern one's own medicine, but e.g., deals with an indication area (to which one's medicine is approved)? There may be other medicines mentioned, but which have a different active ingredient than our medicine.

Answer: *If abstracts do not mention medicines, but e.g., only relates to disease information, or if the medicines referred to have a different active ingredient than one's own medicine, these can be distributed.*

7. The phase III study which is the base for our medicine approval included three arms in which different doses were studied. Only one arm of the study was approved. Does that mean we can't use our Phase III study as a basis for advertising, as it contains unapproved dose information?

Answer: *As a starting point, one cannot use an article if it is based on, or contains, e.g., unapproved doses. It will be possible to use the Phase III trial as long as it is not used to promote the use of a dose other than the approved one. Thus, if it is evident in e.g., an advertisement that the statement (claim) deals with something other than dose, and thus it is clear that one does not use the reference to promote off-label dosing, it may be ok. However, this should, as a rule, be avoided and only the SPC in question should be used.*

8. Can we use a decision from a Swedish court of justice in our promotional material? The decision states that the generic product on the market is not as effective as the original medicine, and we would like to share that message.

Answer*: No, a decision from a court of justice will not be in accordance with Art. 7 (5) of the Promotion Code, on documentation. If you want to say something about the properties of your medicine, you must refer to the approved SPC or scientific studies. If you believe that the decision contains news that has news value, you may consider issuing a press release about it - but not applying the decision in advertising contexts.*

9. Can results from a market survey be used as documentation?

Answer*: It depends on the claim itself. If the claim discloses something about the properties of the medicine, including efficacy and safety profile, the results of market research cannot be used as basis for documentation.*

10. Can we use a supplementary appendix for reference?

Answer: *In the case of supplementary information based on the original article, so that the entire article then consists of the original article plus the appendix, it is ENLI's opinion that the supplementary appendix should be included if one exists. However, the Supplementary Appendix will not stand alone as a reference. Though, without sufficient study information in the advertisement, it will rarely be possible to use an effect measure or other, which is handled solely in the supplementary appendix and does not constitute one of the main messages of the study.*

Factual information

Guidelines

11. If you want to use guidelines in an advertisement, should they be published in peer reviewed journals? Or is it enough that they are on the website of an official medical society?

Answer: *If it involves information on the properties of the medicine, including efficacy and safety profile, only documentation that has been peer reviewed and published in a recognized and independent journal can be used, cf. Art. 7 (5) of the Promotion Code. In such cases, reference may be made to the original article and supplementary to the guideline if it contains the same information. If reference to guidelines is used solely for information on illness, including e.g., diagnosis, there will be no requirement that the guideline be peer reviewed, etc.*

Guidelines cannot be used comparatively, ie. information about 1st choice, 2nd choice, etc. may not be used for promotional purposes. However, the Investigator Panel sees the possibility that guidelines relating to groups of medicine and their eligibility in a disease spectrum can be used. For example, for the area of COPD there are several degrees of disease where a stepwise escalation of treatment, based on the SABA, LABA, LAMA, ICS medicines groups, can occur. The starting point here is that the information from the guideline is based on the medicine groups in various severity of the disease, without specific medicines being used, and if no weighting of the medicine groups is made.

12. When using guidelines: Is there a difference between whether we refer to a product, a medicine class, medicines in general or disease level (often disease background will be included in larger materials)?

Answer: *Yes. Guidelines cannot be used solely as a reference for statements about the properties of the medicine, including efficacy and safety profile. Reference to guidelines can be made or used as a supplemental reference and can only be done if the guideline does not contain off-label mention of the medicine or other information that contravenes the medicine's SPC. Reference can be made to the guideline regarding factual information about the disease, including symptoms and diagnosis.*

13. Can you reproduce exactly what is stated in guidelines (copy/paste) on disease information? Even though one's medicine is recommended in guidelines?

Answer: *If you use the guideline as a reference for illness/health information, you can quote from and direct reference to the guideline. If the guideline is desired to be used to address the properties of the medicine, including efficacy, safety profile, etc., this can only be done as a supplementary reference. In such cases, reference should be made directly to the published scientific study, which must also comply with the requirements of the Promotion Code.*

14. Is there a difference between guidelines from authorities or from medical societies?

Answer: *No, but guidelines must be relevant to Danish clinical practice in order to form the basis for information about the disease, including symptoms and diagnosis. Guidelines should never be used as a direct reference to information on the properties of the medicine.*

15. Is there a hierarchy of guidelines? E.g., that the Danish are better than the Europeans and the Europeans are better than e.g., WHO?

Answer: *No but recognized international or European guidelines on which Danish clinical practice is based must be considered as the most relevant.*

16. In a commercial, can you use a claim that comes from a guideline, but where the claim does not specifically praise one's own medicine, but an entire group? In the guideline, based on a scoring system, limits have been set as to when a patient can be treated with anticoagulants and concluded that patients with atrial fibrillation that are in the right patient group for NOAC, are recommended a NOAC rather than a vitamin K antagonist.

Answer: *The question is how one has come to the conclusion: "In patients with atrial fibrillation who are eligible for a NOAC, a NOAC is recommended in preference to a Vitamin K antagonist."? Is it a conclusion the authors of the guidelines themselves draw on the basis of an interpretation of the scoring system, or is there a scientifically documentable evidence on the basis of the claim? If there is scientific evidence for the statement, this must be referred directly, provided that the documentation complies with the rules of the Promotion Code. A reference to the guideline can be supplemented.*

17. We would like to be able to provide guidelines to doctors - most of all unsolicited. This is a pocket edition of X's guidelines (compiled by X) in just under 60 pages, without references and without off-label mention of our medicines.

Answer*: It will be ok to provide guidelines unsolicited and uncommented if you do not use a guideline in this context to document information about one's medicine (or place the medicine as a better "choice" than competing medicines), but will distribute it to inform about the guideline in itself. In this context, it is important to note:*

- *The guideline must not contain information on one's medicinal product that is in violation of the approved SPC. If the guideline contains information that confirms or clarifies - and is compatible with - the SPC, but is not directly covered by the SPC, references must be provided.*
- *Compulsory text must always be provided when distributed unsolicited, as this is an advertising activity.*

18. As a pharmaceutical company, may we host a continuing education meeting where the applicable guidelines for a given disease area are reviewed by a hired specialist physician?

Answer: *Yes, it is the Investigator Panel's assessment that continuing education events may be held where applicable guidelines within a given disease area are reviewed as described, provided that the review - and the specific guideline - does not contain information on the company's medicines that are in contravention of the approved SPC for the medicine, including approved therapeutic indication, dosages, etc. It is also assumed that statements about the company's medicines in the guidelines used are documented with a reference that complies with the rules of the Promotion Code, including in particular Art. 7(5). It should be noted that the company is responsible for the continuing education meeting and must therefore ensure that the presenter does not mention the company's medicine in violation of the advertising rules.*

Information from the Medicines Council

19. May the entire recommendation from the Medicines Council with a compulsory text on top and nothing else, be handed out?

Answer: *Basically, yes. If the entire recommendation is distributed without further comments, the recipient will receive adequate information on the Medicines Council's assessment of the medicine, including any concerns expressed in this regard. If the recommendation is provided unsolicited to healthcare professionals, it is an advertising activity and therefore a compulsory text must be provided. In this situation, it must also be ensured that the information in the recommendation of the Medicines Council is in accordance with the approved summary of product characteristics of the medicinal product and the approved therapeutic indication for the medicinal product. The distribution must be uncommented and without supplementary material.*

20. We have received a recommendation from the Medicines Council, and we would like to make this known to the doctors by sending them an e-mail with reference/link to the Medicines Council's recommendation. But in this way, the recommendation of the Medicines Council becomes the primary documentation base and thus implicitly a claim. How can you distribute a recommendation without violating the rules?

Answer: *The recommendation of the Medicines Council can be distributed in its entirety if it is done without accompanying comments on the properties of the medicines. See also question 19 and section 6.2.1.*

21. As a follow-up to a sales consultant's visit, can you write an email to the doctor and summarize the points from the meeting as well as refer to the Medicines Council's assessment of the medicine that you reviewed at the meeting?

Answer: *You can do so if the recommendation of the Medicines Council is not the main message of the e-mail. In addition, a link to the entire recommendation should be included in the e-mail to ensure that the information from the Medicines Council on the medicine in the e-mail is adequate. Thus, one must not suffice with an excerpt of the recommendation.*

22. Is it possible to make a banner ad with the text "*The Medicines Council has now approved an indication extension of [medicine]*"?

Answer: *No, that won't be possible. The Medicines Council does not "approve" medicines or indication extensions. It is a matter for the Medicines authorities. In addition, the recommendation of the Medicines Council must not be the primary basis for/only message with a medicine's advertisement. Thus, a recommendation from the Medicines Council cannot be used to make claims of a medicine as in the banner advertisement described.*

23. Is it correctly understood that it is ok with information in an advertisement that a medicine is now on the "Basis List"?

Answer: *Factual information can be referenced in an advertisement, including that a medicine is included in the "Basis List". The "Basis List" can be used as a reference for factual information in the advertisement in the same way as information from the Medicines Council. Thus, the information must not be used to describe anything about the properties of the medicine or to compare the medicine - directly or indirectly - with other medicines. Accordingly, factual information must be kept completely objective and neutral, and thus should not appear in the advertisement in a way that it can be construed as laudatory for the medicine in question.*

Information from other sources

24. Can you refer to factual information (e.g., number of patients) on DANBIO's website? DANBIO, which is a nationwide clinical quality database for rheumatology. The database is based on reporting from staff at the country's rheumatology departments and private clinics. DANBIO is the result of a collaboration between the Danish Rheumatological Society and the Department of Rational Pharmacotherapy. The database is managed by a steering committee with representatives appointed by the Danish Rheumatological Society, Younger Rheumatologists, the Danish Rheumatologists' and Physicists' Organization, and the Danish Regions.

Answer: *A legitimate website may be used as a reference for information about e.g., number of patients with a given disease in Denmark - or other "disease information". Thus, for information that is not medicine-related, a website, such as the one mentioned, could be used for reference.*

However, care should be taken with how to use such information in advertising, as it can be difficult to see what specific data is extracted from their database and whether the extract fits the population of patients in the medicine's target audience.

25. Is it allowed to use the tender prices that can be found on Amgros' supplier portal? The prices, which can be found on the supplier portal, are not available at www.medicinpris.dk, but are available to all relevant parties (healthcare professionals and pharmaceutical companies).

Answer: *Yes, those prices can be used if they represent the prices paid for the hospital-administered medicines and if they are controllable to the recipient of the information.*

Adequate advertising

26. How is it made clear in practice that information from e.g., The Medicines Council's recommendation is used as supplementary and not primary documentation? Should it be written in a special way in the footnote?

Answer: *First of all, such information must not be the primary message of the advertisement. There is no formal requirement for how it should be stated, but it must be secondary to the other medical and relevant information which is the main purpose of the advertisement.*

27. When the reference is the approved summary of product characteristics: Do you simply write "Product summary" or must it be specified with "approved summary of product characteristics" and any date?

Answer: *There is no requirement that reference be made to a dated summary of product characteristics or that "approved product summary" is stated.*

28. Can an electronic advertisement have the additional information about study design, study limitations, etc. via a link from the advertisement - e.g., via a button that says "Study Design and Limitations" - or should such information always appear in the promotional part of the advertisement?

Answer: *The information must appear in the promotional part if it is relevant in order to understand the background to the statements that appear in the advertisement. If the advertisement - without information about study design, etc. - will be misleading, such information must thus appear directly in the promotional part of the advertisement. If the promotional part is complete without additional information on study design, these can be referred via link.*

Real World Data

29. We find that the authorities are increasingly calling for Real World Data studies, and therefore there will also be a greater use of RWD studies in promotional materials. You write that RWD studies should be put in the context of RCT studies. Can this be done by, for example, presenting the RCT study first, and then a presentation of RWD data (if RWD only confirms/supports the RCT study) and new claims are not used, only supporting claims?

Answer: *Yes, it will be a way to relate RWD data to the RCT study for which the medicine is approved on.*

30. In connection with a continuing education meeting organized by the pharmaceutical company, may a presentation be made to physicians, presenting only an RWD study, but not directly in conjunction with the medicine's SPC or the RCT study for which the medicine is approved?

Answer: *When presenting Real World Data (RWD) in promotional material, this should be predominantly put in a context of data from randomized clinical trials (RCTs). See AN-2017-1490, as well as above under section 6.4.*

Comparative advertising

31. Can medicine A be compared to medicine B from data in a new head-to-head study, although this comparison is not mentioned in the SPC (in the SPC, medicine A is compared to medicine C), but the indication, dose and patient population are according to the Summary of Product Characteristics for medicine A and B?

Answer: *Yes, it will be possible if the requirements for the documentation are met. The new study can be seen as a supplement to data in the SPC and may be relevant to the therapeutic area. This is also in line with the Appeals Board's statement in AN-2012-2713, according to which comparative advertising based solely on the SPCs will not always be sufficient if new relevant data is available.*

32. If we compare our medicine A with the competitor's medicine B in a head-to-head study, what would it mean, that the results of medicine B in the head-to-head study are not in accordance with the SPC for medicine B? I.e. can one as a pharmaceutical company be held responsible for presenting data in a comparison that does not comply with the competitor's SPC?

Answer: *In principle, comparative advertising must be based on the information contained in the SPCs. The comparison must only include medicinal products that are relevant to compare from an objective point of view, i.e. medicines with the same scope. Therefore, it is not possible to promote data where the competitor's results are not in accordance with its medicine's summary of product characteristics, including approved therapeutic indication.*

33. Can RWD studies be used to compare efficacy or other endpoints between medicine A and B?

Answer: *Danish law does not require only the use of RCT studies as documentation. Basically, a study can be used in advertising if it is scientific research and has been published in established and independent Danish or foreign professional journals or the like, and before publication has been subject to independent review (peer review).*

In many therapeutic areas, there is a lack of head-to-head RCTs, and it can thus be useful to make comparisons on RWD data. However, claims cannot be "as direct" as when based on RCTs and the information in the comparison should be more elaborate - so that they are proportionate to the degree of evidence of the study. Furthermore, the advertisement should not be based solely on the RWD study.

Advertising should therefore reflect the degree of evidence (ranking in the evidence hierarchy), both in terms of the wording of claims and in terms of the increased need for additional information about the study, design, limitations, etc. This information must be given directly in relation to the advertisement - close to the claim, so that the healthcare professional can easily understand the claim in relation to the degree of evidence of the reference.

34. If the company that prepares a price comparison has confidential prices, but the medicine that is compared can be found on Amgros' supplier portal, can the company then compare the prices i.e. use its own confidential price and compare with the tender price of another medicine?

Answer: *If the company publishes a price comparison to healthcare professionals, the prices will no longer be confidential.*

35. At the request of a healthcare professional, can an analysis be made based on AIP prices (from www.medicinpris.dk) with the possibility that the healthcare professional can insert his purchase prices himself?

Answer: *Yes, that could be possible.*

10. Check list regarding information material and documentation

- Basic requirements for medicines advertising:
  - Must be adequate
    - Must, among other things, contain adequate information for the recipients to understand and assess when and in what situations the medicine may/may not be used
  - Must be factual
    - Must not be marketed as aggressively as regular consumer goods
    - Must be based on professional and relevant information
  - Must not mislead or exaggerate the properties of the medicine
    - Must not have a design and content that may give the recipients a false understanding of the medicine, illness or treatment
    - The advertisement must not place the medicine in a more favorable light than other similar medicines
  - Information in the advertisement must be in accordance with the approved product summary of the medicinal product.

- Information on the properties of the medicine, including efficacy and safety, must be substantiated by scientific data from the medicine's approved SPC or from scientific studies published in established and independent Danish or foreign works, professional journals, etc. The studies must have been subject to an independent assessment prior to publication.

- The degree of evidence of the source must be assessed in relation to the informational need of the specific advertisement.

- Essential information must be found in the promotional part of the advertisement so that there is no risk that the information in the advertisement will mislead the reader

For further information:

ENLI: www.enli.dk/en

Danish Medicines Agency: www.dkma.dk

Appendix A

Examples on using documentation

1. Medicines Council

As mentioned in section 6, it will not suffice simply to mention that the medicine is "*Recommended by the Medicines Council as standard treatment*". Thus, reservations and concerns must also be included in order for the advertisement to be considered to contain adequate information.

For the medicine below, an information in the medicine's advertisement that the medicine is recommended by the Medicines Council should thus contain all the information from the recommendation:

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1. The Medicines Council's recommendation

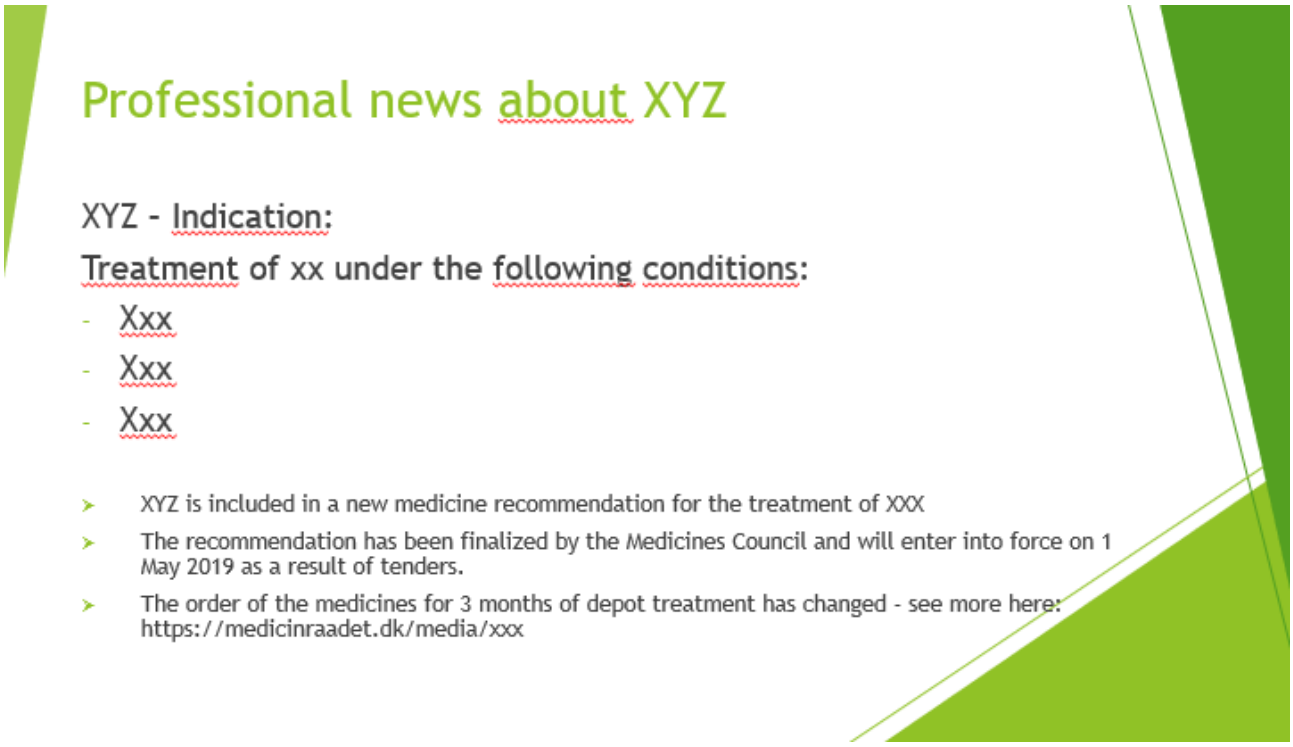
The Medicines Council recommends [medicine X] as standard therapy for patients with [Y] who have first-line disease activity, including patients with particularly high disease activity who have not previously been treated. [Medicine X] is recommended for the following populations, taking into account the following concerns:

- Patients who are […] positive
- Patients who are […] negative
- Patients where treatment with […] or […] is not an option.

The Medicines Council expresses concern about the long-term effect of [medicine X] which could potentially put patients with disease breakthroughs after two years in a situation where they cannot be offered any other relevant second-line treatment. In addition, the Medicines Council expresses concern about late adverse reactions. It is emphasized that no position has been made on the placement of [medicine X] in relation to the other approved medicines.

Instead of a longer citation of the Medicines Council's recommendation, one can briefly refer to the fact that one's medicine has been assessed by the Medicines Council, but not in more detail about the recommendation of the Medicines Council. See the example below, section 1.1.

1.1. Legal reference to recommendations (fictitious medicine "XYZ")



In this example, the Medicines Council's recommendation is not used as the primary element in the advertisement, and no mention is made of what the Medicines Council has recommended. The advertisement, in the opinion of the Investigator's Panel, shows factual information that the medicine has been reviewed by the Medicines Council. A design such as this is, in the opinion of the Investigator's Panel, in principle in accordance with the rules on documentation.

2. Guidelines

Example of reference to guidelines on a 1-page fact sheet on the medicine:

1-page fact sheet on a clinically published study on product X used for Y indication and with mention of guidelines at the bottom