

**Report on
”Medicines most frequently involved in
serious adverse drug events”**

Prepared by the ‘High-alert medicines’ working group 2008-10

**The Danish Medicines Agency’s
‘Prevention of Medication Errors’ Network**

Copenhagen, 2011

Foreword

In 2008, the Danish Medicines Agency established a working group under the ‘Prevention of Medication Errors’ network to prepare proposals for defining and listing high-risk medicines.

As an authority, the Danish Medicines Agency has a duty to act on potentially problematic issues and point out any challenges related to the use of certain medicines in specific situations. This report includes all serious adverse events, also where only one serious adverse event has been reported, as this is deemed sufficient to be included as source material. Serious events are events which have resulted in hospitalisation, prolonged hospitalisation or death.

The purpose of the initiative was to identify those medicines posing a special risk to patients based on preventable adverse drug events (pADEs). Incorrect use of these particular medicines may have health consequences for the individual patient and potentially result in additional costs for society. Both reporting systems and scientific studies indicate that these specific medicines are involved in adverse events resulting in acute hospitalisation, prolongation of existing hospitalisations or other serious events.

The working group has taken a broad approach to the issue and has come across a large number of warning systems intended to warn against and limit specific types of pADEs; some medicines, for example, must be prescribed using special prescription forms to limit abuse. Other medicines are subject to very special requirements for follow-up on potential risks. These so-called risk-reduction measures are applicable right from the date of marketing. Other medicines have a warning included in the summary of product characteristics stating they should not be used for specific patient groups, e.g. pregnant women. A significant part of the task has thus been to provide a practical definition of the high-risk medicines concept, a task which, also upon the completion of this report, is likely to continue in the future work with patient safety.

This report contains the working group’s proposed definition of the ‘*medicines most frequently involved in serious adverse drug events*’ concept. This terminology has been selected to clearly signal that it is not the medicine *per se* which poses a risk, but rather the medicine seen in context of the situation in which it is handled to the same extent the situations in which the medicine is handled.

The work has resulted in two lists of *medicines most frequently involved in serious adverse drug events*, listed by active substance and medicine group, respectively. The lists have been prepared in sortable spreadsheets so that they can also be grouped according to the situations and routines during which the adverse events have occurred.

The Danish Medicines Agency would like to extend its thanks to the working group members for their efforts. Chaired by Annemarie Hellebek, the working group consisted of the following members: Bente Dam, Christianna Marinakis, Dorte Glintborg, Karin Povlsen, Linda Aagaard Thomsen, Majken Nørskov Petersen, Malene Vestergaard, Marianne Lisby, Marie Lund Nielsen, Steffen Thirstrup, Thalia Blicher and Marie Melskens.

We hope that this work will serve as a tool for all those working with medicines in the health sector and that it will contribute to improving patient safety.

Danish Medicines Agency, June 2011

Summary

In autumn 2008, the Danish Medicines Agency established a working group under the ‘Prevention of Medication Errors’ network to define the ‘high-risk medicines’ concept and identify these medicines.

During the process, the working group reached the conclusion that the term ‘high-risk medicines’ does not fully cover those medicines which, in combination with a specific situation, pose a special risk of patient injury. Instead, the working group has decided to use the ‘*medicines most frequently involved in serious adverse drug events*’ concept.

The working group intended to provide a knowledge base of these medicines and the situations which involve special risks for patient safety for all relevant players in municipalities, regions and authorities in Denmark.

Proposal for national definition of *medicines most frequently involved in serious adverse drug events*

Medicines most frequently involved in serious adverse drug events are medicines which have de facto caused preventable adverse events of a serious nature as a result of either:

- the medicine’s pharmacological property (e.g. a narrow therapeutic index)
- errors in the medication process (inappropriate handling of the medicine by healthcare professionals)
- inappropriate medication use (by patient)

Adverse events of a serious nature are events which have resulted in hospitalisation, prolonged hospitalisation, need for acute life-saving treatment, permanent injury or death.

Medicines most frequently involved in serious adverse drug events are not the same as medicines with a risk management plan with special conditions. In connection with the authorities’ approval procedure, it has been assessed that the latter medicines must be subjected to specific risk reduction measures. These measures are implemented based on the assumed risk associated with the use of the medicine, independent of the situation in which they are handled.

Proposal for list of *medicines most frequently involved in serious adverse drug events*

A review of literature and databases has shown that it is predominantly the same medicine groups which have been involved in adverse events from the 1970s and up until today.

The medicines were identified by reviewing literature covering both the primary and the secondary sectors as well as by reviewing SAC score 3 adverse events from the Danish Patient Safety Database (DPSD) and published cases from the Danish National Agency for Patients’ Rights and Complaints. The working group has decided to include all medicines which have resulted in at least one factual serious adverse event described in either a spontaneous report to the DPSD, a case submitted to the

Danish National Agency for Patients’ Rights and Complaints or a epidemiological study.

The source material for the report is based on systematic survey articles and descriptive epidemiological studies concerning the primary and secondary sectors (published up until 2008), published cases from the Danish National Agency for Patients’ Rights and Complaints (up until 2010) and serious adverse events in the Danish Patient Safety Database (up until 2010).

As mentioned above, the evidence basis for identifying the *medicines most frequently involved in serious adverse drug events* includes, among other things, spontaneous reports in which risk managers employed in the regions have assessed reported events in the secondary sector in terms of causality and severity. The working group has reassessed factual SAC score 3 events from the DPSD before the medicines were assessed as candidates for the list of *medicines most frequently involved in serious adverse drug events*.

The process of identifying high-risk situation medicine candidates has resulted in two lists: i) a list of active substances (Table A) and ii) a list of medicine groups (Table B). In those cases where only special formulations of the active substance have shown to pose a risk, such pharmaceutical forms have been linked to the active substance on the list (Table A).

Table A. Medicines most frequently involved in serious adverse drug events active substances listed in alphabetical order (the pharmaceutical form is listed if relevant).

Active substances
Acetylcysteine, concentrate for solutions for infusion ⁵
Amiodarone ^{5, 27}
Digoxin ^{5, 27, 30, 49, 53, 70, 72, 75, 77, 81, 91, 93, 94}
Epinephrine (adrenaline) ^{27, 69}
Ferri-salts, injection fluid ⁶⁹
Fosphenytoin ⁵
Glucose ^{5, 68, 69}
Glyceryl trinitrate ⁵
Lidocaine ⁵⁴
Levothyroxine ⁶⁸
Methadone ^{5, 68}
Metoprolol ^{5, 30, 79}
Nifedipine ⁴²

Norepinephrine (noradrenaline) ^{5, 69}
Phenobarbital ^{27, 69}
Phosphate, concentrate for solution for infusion ⁵
Phytomenadione (Vitamin K ₁) ⁶⁹
Potassium, mixture and concentrate for solution for infusion ^{27, 42, 69}
Prednisolone ^{30, 73, 74}
Propofol ⁶⁹
Sodium polystyrene sulfonate ⁴²
Suxamethonium ¹⁰¹
Thiopental ⁵

The identified medicine groups are shown in Table B. Specific active substances and subgroups identified in case reports or by literature review are stated in a parenthesis after the medicine groups.

Table B. Medicines most frequently involved in serious adverse drug events groups listed in alphabetical order.

Medicine groups (specific active substances and subgroups)
Antibiotics (amoxicillin, ceftriaxone, cefuroxime, ciprofloxacin, gentamicin, nevirapine, penicillin) ^{5, 42, 50, 53, 68, 69, 79, 82, 93, 99, 100}
Antidepressants (SSRI) ^{96, 97, 98}
Antipsychotics (haloperidol, quetiapine, zuclopenthixol) ^{5, 42, 53, 68, 73, 86, 95, 96, 97, 102, 103, 104, 105}
Antithrombotics and coagulation inhibitors (acetylsalicylic acid ^a , clopidogrel, enoxaparin, phenprocoumon, tinzaparin and warfarin) ^{5, 27, 30, 42, 51, 52, 53, 68, 69, 72, 73, 74, 75, 77, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92}
Benzodiazepines (midazolam, triazolam) ^{42, 53, 68, 78, 79, 80, 85, 88, 96, 97}
Cytostatics (carboplatin, daunorubicin, etoposide, 5-fluorouracil, methotrexate) ^{5, 27, 42, 68, 69}
Diuretics (furosemide, thiazide diuretics ^a) ^{5, 53, 70, 71, 72, 73, 74, 78, 81, 82, 84, 85, 86, 92, 95, 96, 97, 98}

Insulin 5, 27, 42, 53, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79

NSAIDs 27, 53, 54, 72, 73, 74, 82, 91

Strong opioids (morphine, oxycodone) 5, 27, 50, 51, 54, 68, 69, 73, 78, 80, 90

^a Mainly related to dose for elderly people.

High-risk situations and medicines

The working group has reached the conclusion that it is not possible to view the medicine in isolation, but that it must be linked to the specific situation in which an adverse event has occurred. The spreadsheet accompanying this report shows significant high-risk situations identified.

Perspectives

The working group hopes that those involved in the practical work in the health sector will be able to use the definition and the list as a basis for their own work with risks related to the medication process. In this context, the list should be regarded as an all-inclusive list which can be adapted to the requirements of each individual site and, for example, be attuned with the site’s recommendation list and medication guides.

In addition, the working group proposes a number of potential initiatives at national level which can improve the monitoring of the risks identified as well as limit the occurrence of new risks:

1. Better registration of serious medication errors for the purposes of learning

The working group recommends that a common national classification of medication errors be prepared and that a shared (anonymised) database containing events from both the Danish National Agency for Patients’ Rights and Complaints (DPSD) and the Danish Patient Insurance Association be established. This will increase the opportunity to monitor *medicines most frequently involved in serious adverse drug events* and high-risk situations and may thus contribute to targeting patient safety initiatives.

2. Ongoing identification of potential *medicines most frequently involved in serious adverse drug events*

The working group recommends that the proposed list be regularly updated through screening of data from the DPSD, the Danish National Agency for Patients’ Rights and Complaints, the Danish Patient Insurance Association, the Danish Medicines Agency’s Pharmacovigilance and published literature.

3. Dissemination of the list of *medicines most frequently involved in serious adverse drug events*

The working group finds that the list of *medicines most frequently involved in serious adverse drug events* should be included in both both pre and postgraduate training of

healthcare professionals in the form of specific teaching material. It is proposed that this teaching material be integrated in pharmacology training courses. The working group also recommends that a campaign on *medicines most frequently involved in serious adverse drug events* be launched and that the report and the list be translated into English and launched at European level to other medicines agencies and patient safety organisations.

4. *Medicines most frequently involved in serious adverse drug events committee*

The working group recommends that a permanently anchored committee be established with the responsibility of updating the proposed list of *medicines most frequently involved in serious adverse drug events* (described under item 2) as well as for developing specific information material to reach the target groups (described under item 3). This committee will also be able to contribute to preparing an error and injury classification (described under item 1).

Contents

Foreword	2
Summary	4
Contents	9
The ‘high-risk medicines’ concept.....	12
Considerations about the definition of <i>medicines most frequently involved in serious adverse drug events</i>	14
Severity	15
Frequency.....	15
Preventability	16
Documentation.....	16
Inappropriate handling and use	17
Method of the working group	19
Delimitation	20
Excluded medicines	21
Preparation of the list	22
Sources	23
Epidemiological studies	23
Databases and other published case reports	24
List of <i>medicines most frequently involved in serious adverse drug events</i>	25
High-risk situations and medicines	27
Discussion	29
Proposals	30
List of definitions.....	32
References.....	35
Appendix 1 Medicines with a risk management plan with special conditions (20 September 2010)	41
Appendix 2 Severity of adverse drug events	43
Appendix 3 Literature review	46
Appendix 4 All-inclusive list of <i>medicines most frequently involved in serious adverse drug events</i> ...	50
Appendix 5 Clarification of the concept of ‘adverse event’ within the pharmaceutical area	51
List of abbreviations.....	53

Purpose

Adverse drug events (ADEs) are the type of adverse events most commonly registered in Denmark. In 2010, 10,188 medication error reports were registered in the Danish Patient Safety Database (DPSD) (corresponding to 30% of all 34,418 adverse events reported), 35 of these being reports with SAC score 3¹. Due to the high number of medication error reports, it is necessary to assign priority to the preventive efforts, including whether specific medicines handled in a particular situation involves special risks in terms of patient safety.

There is also a strong desire from healthcare professionals, lecturers, providers of information on medicines, authorities and private players in the area of medicine for initiatives to prevent medication errors and that these initiatives be based on the medicines posing the highest risks to the patient. Most recently, the US organisation Institute of Health Improvement has recommended that hospitals identify and take initiatives aimed at high-risk medicines (high-alert medications) to increase patient safety at hospitals².

The purpose of this report is to provide a knowledge base of medicines which involve special risks for patient safety for all relevant players in municipalities, regions and authorities. The purpose of the report is also to present a proposal for a national definition of ‘*medicines most frequently involved in serious adverse drug events*’ and prepare a proposal for a list of *medicines most frequently involved in serious adverse drug events*. Currently, no similar work exists at European level, and the report is thus also expected to be used to promote knowledge of *medicines most frequently involved in serious adverse drug events* in the EU.

The target group for the work includes:

- 1 Healthcare professionals in the primary and secondary sectors:
 - doctors in connection with prescription and monitoring of *medicines most frequently involved in serious adverse drug events*
 - pharmacy pharmacists, pharmacy technicians, nurses, social and healthcare assistants as well as social and healthcare helpers in connection with dispensing and administration of *medicines most frequently involved in serious adverse drug events*
 - clinical pharmacologists, clinical pharmacists and others involved in spreading the knowledge of and limiting the incidence of serious ADEs.
- 2 Central players in the area
 - authorities such as the Danish Medicines Agency and the National Board of Health
 - regions
 - municipalities
- 3 Suppliers
 - providers of information on medicines
 - medicine distributors
 - The pharmaceutical industry

The source data of the report will be based on documented adverse drug events.

It is important to distinguish between *medicines most frequently involved in serious adverse drug events* and existing medicines with a risk management plan. *Medicines with a risk management plan with special conditions* (Appendix 1) are selected during the authorities’ approval procedure based on an assumed risk associated with the use of the medicine. The marketing authorisation holder must pay extra attention to this medicine in relation to, for example, adverse drug reactions and interactions. *Medicines most frequently involved in serious adverse drug events*, with which this report is concerned, are identified *after* the marketing of the medicine based on inappropriate handling or use of the medicine which *has* caused one or more factual adverse events (case reports and epidemiological studies) having a serious clinical consequence.

The working group

The ‘High-alert medicines’ working group was established in September 2008 within the Network for the Prevention of Medication Errors, under the Danish Medicines Agency. Representing different professional organisations, research institutions and authorities, the members of the working group possess clinical pharmacology knowledge of medicines and/or practical medication experience. The working group has members from both the primary and the secondary sectors (Table 1).

The terms of reference for the working group were as follows:

- 1 Taking as a starting point applicable literature and experience from existing initiatives on high-risk medicines.
- 2 Preparing a proposal for a national definition of high-risk medicines.
- 3 Preparing a proposal for a national list of high-risk medicines.
- 4 Disseminating knowledge of the material prepared.

The working group held a total of seven meetings to define the *medicines most frequently involved in serious adverse drug events* concept, to gather and organise data, to choose selection criteria as well as to prepare two lists of *medicines most frequently involved in serious adverse drug events* –one listing active substances and one listing medicine groups.

The prepared definition and list have been presented to the Network for the Prevention of Medication Errors. The final result is presented in the form of this report.

Table 1 Overview of working group members

Members of the working group:	Appointed participant for:
Annemarie Hellebek (chairman)	Danish Medical Association
Bente Dam	Amgros
Christianna Marinakis	Danish Drug Information
Dorte Glintborg	Institute for Rational Pharmacotherapy
Karin Povlsen	Danish Medicines Agency Formerly the National Board of Health
Linda Aagaard Thomsen	Pharmakon, education and training centre of the pharmacies, representative for the Association of Danish Pharmacies
Majken Nørskov Petersen (withdrew during the process)	Capital Region Pharmacy, representative for Association of Hospital Pharmacies in Denmark
Malene Vestergaard	Danish Society for Patient Safety
Marianne Lisby	Danish Nurses’ Organization
Marie Lund Nielsen (withdrew during the process)	Region of Southern Denmark, representative for Danish Regions
Marie Melskens	Danish Medicines Agency
Steffen Thirstrup	Danish Medicines Agency Formerly Institute for Rational Pharmacotherapy
Thalia Blicher	Formerly Institute for Rational Pharmacotherapy

The ‘*medicines most frequently involved in serious adverse drug events*’ concept

The working group has examined which terminology and associated definitions international and national organisations use for the Danish concept of ‘risikolægemidler’ (high-risk medicines). During the preparation of a Danish definition, the working group has on several occasions discussed which terminology would be the optimal solution in Danish.

- Internationally, the terms ‘high-alert medication’ and ‘high-risk medication’ are used for the Danish term ‘risikolægemiddel’ (see the section ‘*Considerations about defining medicines most frequently involved in serious adverse drug events*’).
- A report on medication errors published by the Council of Europe in 2006³ with authors from a number of European countries uses both terms, ‘high-risk medication’ and ‘high-alert medication’, but the concepts have not been used consistently throughout the report.
- The British National Patient Safety Agency (NPSA) uses neither of these concepts in its most recent list of medication errors. Instead, the NPSA has a list of ‘medicines most frequently

associated with the most severe harm’⁴.

- In Denmark, the National Board of Health published a theme report (in Danish) on high-risk medicines (‘Risikomedicin’⁵) in 2007. The report states that no unambiguous definition of high-risk medicines exists. The report is an analysis of ADEs in the DPSD reported as ‘SAC score 3 AEs’, meaning that they had factual or potential serious consequences for the patient.
- Up until 2008, the United States Pharmacopeia (USP) operated a reporting system for pADEs. In certain reports, the USP stated that ‘high-risk medication’ was medicines involving serious injury in more than 6% of the reports⁶. This definition has not been found elsewhere, and the working group has not found this frequency useful for its definition as it is known today that the number of reported events varies considerably.
- The Institute for Safe Medication Practices (ISMP) organisation operates the largest US reporting system for pADEs. The ISMP deliberately uses the concept ‘high-alert medication’ instead of ‘high-risk medication’, as they argue that the concept of ‘risk’ normally requires that a specific frequency can be calculated. Frequency may, for example, be expressed as the number of ADEs in relation to the total number of AEs or in relation to the consumption of the given medicine in the health sector in question.

Among the international concepts, only the USP has attempted to use a denominator in its definition of a high-risk medicine. The working group would like to relate the high-risk medicines concept to the frequency of ADEs in relation to the number of users and the duration of their treatment (person-years) or in relation to the total number of AEs. The Danish Medicines Agency has access to information about consumption and the number of users of prescription-only medicines in the primary sector. As regards the secondary sector, the Agency has access to information about the consumption of medicine but not the number of users in person-years. At present, it is thus not possible to state the specific frequency of pADEs in relation to the number of users in person-years. Nor is it possible to relate the incidence of serious pADEs to the total number of pADEs as this number varies depending on the reporting frequency of healthcare professionals. In the opinion of the working group, there is considerable scope for developing methods for assessing the frequency of serious pADEs.

The international definitions of high-alert medication clearly take the term ‘medicine’ (medication) as their starting point.

Following discussions on the terminology, the working group has decided to not only focus on the risks associated with a medicine, but also on the situations involving the risk of errors. The working group has thus decided to introduce the concept of ‘*medicines most frequently involved in serious adverse drug events*’ (‘risikosituationslægemidler’ in Danish).

The working group therefore finds that pADEs may occur when at least one of the following factors poses a challenge:

- Patient
- Medicine

- Handling

Challenges posed by the *patient* include, for example, that the dosage of a medicine will differ for children, elderly people, pregnant women, persons with liver or renal failure etc. and that patient compliance is of importance.

Challenges posed by the *medicine* include, for example, that some medicines may have a narrow therapeutic index, a teratogenic effect, a special potential for abuse etc. The circumstances relating to risks associated with the medicine itself are assessed in the approval procedure in connection with the manufacturer’s preparation of a risk management plan for the medicine. In the event of serious risk factors, the medicine’s risk management plan will be subject to special conditions. Medicines involving a special potential for abuse are monitored by applying section 4 of the Danish executive order on prescriptions⁷.

Challenges posed by the *handling* include, for example different dosage frequency, the need for special calculations or the need for dosage escalation or reduction tables.

In preparing the report, the working group has placed significant emphasis on the interplay between these three factors. Examples of challenges posed by the interplay of patient, medicine and handling include calculation errors in connection with dosing for children, confusing mg with the number of tablets or dosing of insulin or heparin calculated on the basis of clinical data.

Considerations about the definition of *medicines most frequently involved in serious adverse drug events*

The working group has discussed the various international definitions and the definition of *medicines most frequently involved in serious adverse drug events* in relation to the concepts of severity, frequency, documentation and inappropriate handling and use.

The ISMP’s definition of ‘high-alert medications’ is closely related to medicines with a narrow therapeutic index (Table 2). This list is based on reports on adverse events in the literature and input from general practitioners and expert statements⁸.

Table 2. International definitions of ‘high-alert medications’.

Source	Definitions
ISMP	“High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error. Although mistakes may or may not be more common with these drugs, the consequences of an error with these medications are clearly more devastating to patients.” ^{8, 9, 10}
JCAHO	“High-alert medications are those medications involved in a high percentage

of errors and/or sentinel events as well as medications that carry a higher risk for abuse or other adverse outcomes”¹¹.

The US accreditation organisation the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has published a definition of ‘high-alert medication’ based on the risk of injury and on reported adverse events¹¹.

JCAHO states the following criteria for high-alert medicines:

- Medicines with a narrow therapeutic index
- Euphoriant substances
- Non-approved or recently approved medicine from the Food and Drug Administration, USA
- Psycholeptics
- Look-alike/sound-alike medicines

In the opinion of the working group, the ISMP’s definition is too narrow and there is not full agreement between the definition and the list on the ISMP website as the ISMP’s list also includes medicines not having a narrow therapeutic index.

The working group finds the JCAHO’s definition too broad, and the different criteria do not appear to be exhaustive.

The working group has thus decided that a Danish definition should be based on severity, frequency, preventability, documentation as well as inappropriate handling of medicine by healthcare professionals and lack of patient compliance.

Severity

To be a *medicine most frequently involved in serious adverse drug events* candidate, the medicine must, according to the working group, have been the main cause of serious patient injury following inappropriate handling. In its assessment of severity, the working group has considered the different classification types of ADE severity (Appendix 2) and has found that only medicines which have caused hospitalisation, prolonged hospitalisation, need for acute life-saving treatment, permanent injury or death should be included in the list of *medicines most frequently involved in serious adverse drug events*. This interpretation of severity is able to contain the existing criteria found in epidemiological studies and in the DPSD’s SAC scoring. The delimitation is also in agreement with the ISMP’s and the JCAHO’s definitions of high-risk medicines.

Frequency

The working group has discussed whether the frequency of adverse events could be included as part of the definition. The estimation of frequency is complicated by the fact that it has been necessary to search for candidates in both epidemiological studies and spontaneous reporting (case reports). Spontaneous reporting is associated with major underreporting, and the number of reports thus cannot

be seen as expressing the frequency of the event. On the other hand, some kind of frequency can usually be estimated from the epidemiological studies, but only very few articles relate the number of events to the consumption of the medicine in question.

As a result of the uncertainty as to the frequency data, the working group has decided to include all medicines which have caused at least one pADE. As regards the epidemiological studies, the working group has made a specific assessment of all candidates and excluded medicines with unclear documentation, see the section ‘Excluded medicines’. At the same time, in a spreadsheet version of the list of *medicines most frequently involved in serious adverse drug events*, the working group has decided to point out if several similar events have occurred and from which source type the knowledge about the medicine originates (case report or epidemiological study).

Preventability

When working with patient safety, a distinction is made between preventable adverse events (can be avoided in future by learning from the event) and non-preventable (cannot be avoided, at least not within the framework of rational pharmacotherapy). The working group has included preventable in its definition to point out that the definition of *medicines most frequently involved in serious adverse drug events* does not comprise medicines with a potential for serious unpredictable adverse drug reactions such as an allergic reaction the first time a patient is given penicillin. To prevent such an event, it would be necessary to remove all penicillin products from the market, which would be unreasonable. Events such as this caused by rare adverse drug reactions which are unpredictable for the individual patient are thus not comprised by the definition. However, had the patient earlier suffered a serious allergic reaction to penicillin, it is a different situation, as it would then be possible to prevent a new adverse event by giving the patient another antibiotic. Such an event is thus comprised by the definition. Another example could be the very rare but serious adverse drug reaction Steven Johnson Syndrome which may result from even short-term treatment with ibuprofen (unpredictable for the individual patient and thus non-preventable). A bleeding ulcer in a patient with a previous history of ulcers, could, on the other hand, be prevented by giving the patient ulcer medicine together with ibuprofen or by giving the patient paracetamol instead.

Documentation

A medicine included in the list must have caused one or more factual and documented serious pADEs. This requirement differs from the ISMP’s and the JCAHO’s definitions which do not include a specific documentation requirement. For Danish healthcare professionals to accept the *medicines most frequently involved in serious adverse drug events* concept and the actual list, it is important, in the opinion of the working group, that the inclusion and exclusion of candidates for the list is widely documented.

The working group has decided that the inclusion requirement for documentation should be one (or more) of the following:

- At least one report in the DPSD (SAC score 3) or from the Danish National Agency for

- Patients’ Rights and Complaints or at least one case report published in a scientific journal.
- At least one inclusion in an epidemiological study published in a scientific journal stating which medicine was involved, the severity degree and that the event was assessed to be preventable.
 - At least one inclusion in scientific articles (systematic reviews, descriptive epidemiological studies and other types of studies) documenting serious patient injury – which could have been prevented – as a result of the medicine’s pharmacological property, e.g., a narrow therapeutic index or use in a particularly vulnerable patient group.

Regional risk managers assess the severity degree of the AEs and score the individual event in the DPSD. The working group is aware that regional risk managers do not necessarily score medication errors in the DPSD in the same way – even the more experienced risk managers can score events relating to factual severity in SCA score system differently. This means that the working group has reassessed factual SAC score 3 events from the DPSD before the medicines were assessed as candidates for the list of *medicines most frequently involved in serious adverse drug events*. The same problem will presumably apply to the future severity classification system in the DPSD (Appendix 2).

The working group is furthermore aware that published data from the Danish National Agency for Patients’ Rights and Complaints do not allow for automatic searching of ADEs, and there may thus be pADEs which the working party has not found.

The source material for the report is based on systematic survey articles and descriptive epidemiological studies concerning the primary and secondary sectors (published up until 2008), published cases from the Danish National Agency for Patients’ Rights and Complaints (up until 2010) and serious adverse events in the Danish Patient Safety Database (up until 2010).

Inappropriate handling and use

The working group has decided that the definition must cover both inappropriate handling of medicine by healthcare professionals and inappropriate patient use. This should be seen in light of the fact that Denmark focuses heavily on compliance and the patient safety risks resulting from lack of compliance.

Proposed definition

The working group proposes the following definition:

Medicines most frequently involved in serious adverse drug events are medicines which have de facto caused preventable adverse events of a serious nature as a result of either:

- the medicine’s pharmacological property (e.g. a narrow therapeutic index)
- errors in the medication process (inappropriate handling of the medicine by healthcare professionals)
- inappropriate (patient) use

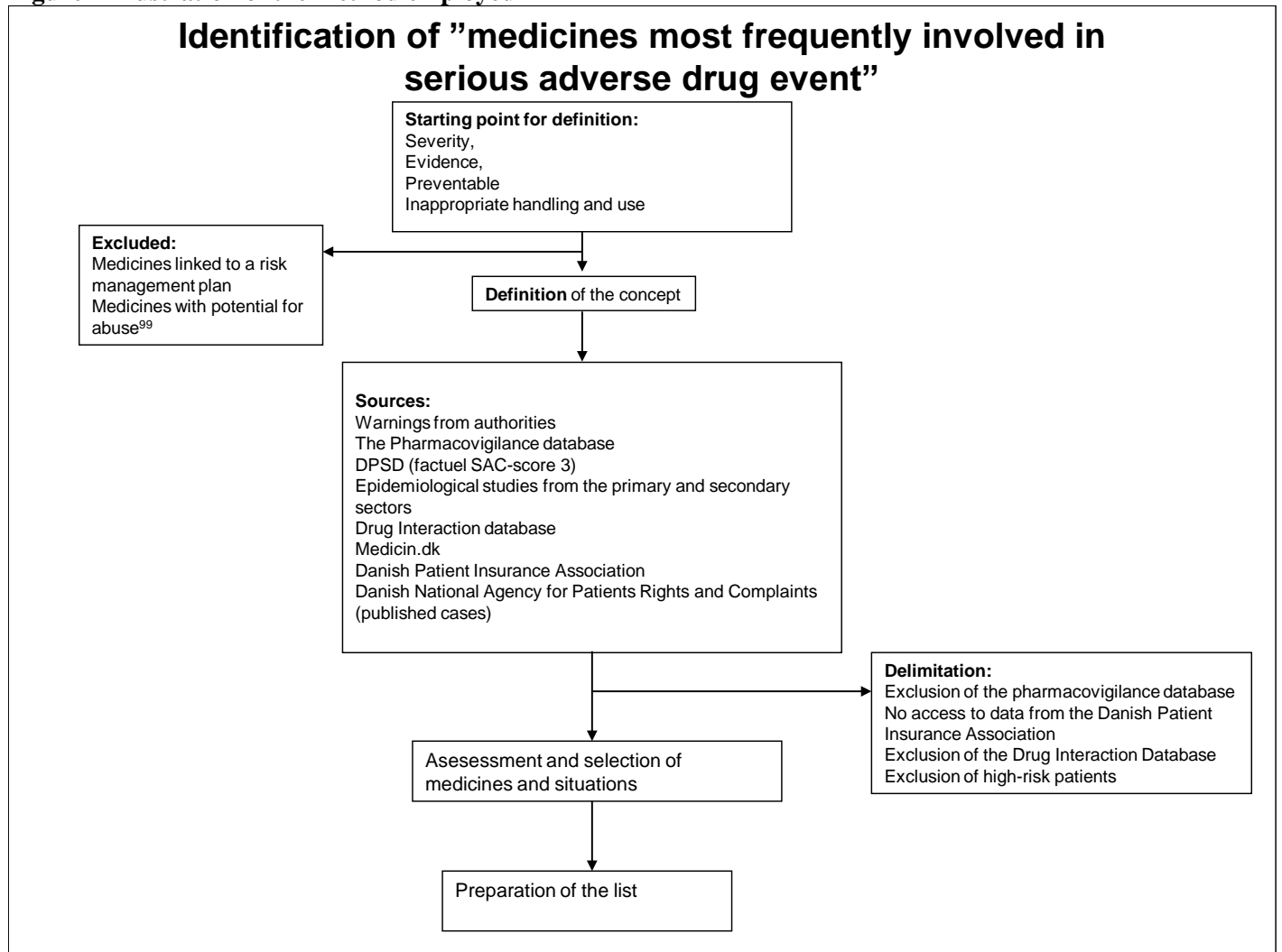
Serious adverse events are events which have resulted in hospitalisation, prolonged hospitalisation, need for acute life-saving treatment, permanent injury or death.

The three criteria in the definition are weighted equally.

Method of the working group

Figure 1 shows the method employed by the working group to identify medicines for the list of *medicines most frequently involved in serious adverse drug events*.

Figure 1 Illustration of the method employed



Delimitation

The working group has decided to delimit the method so that the following information is not included as source material for the extraction of potential medicines for the working group’s list of *medicines most frequently involved in serious adverse drug events*:

- 1 The pharmacovigilance database
- 2 Patient insurance data
- 3 Medicines associated with a risk management plan with special conditions
- 4 Risk patients and contraindications
- 5 The Drug Interaction Database
- 6 Intended event

The pharmacovigilance database¹² has not been used as it is based on information related to *appropriate use* of the medicine within the recommended dosage interval, as opposed to the definition of *medicines most frequently involved in serious adverse drug events* which concerns *inappropriate use* of the medicine. The information in the pharmacovigilance database cannot be used to illustrate how dangerous the medicines potentially are when used inappropriately, but it describes the types of adverse drug reactions which the patient may suffer. A causality assessment is made of serious adverse drug reactions.

Patient insurance data¹³ have not been used, as only examples of decisions are published to show the current practice within the area.

In connection with the approval of new medicines or the updating of the product information for existing medicines, the manufacturer of the medicine must assess whether the medicine poses a risk of medication errors, e.g. due to its name, appearance or labelling. The assessment appears from the medicine’s risk management plan (EU-RMP)^{14 15}. If risk reduction measures are required, which would, for example, apply to medicines with a known teratogenic effect such as thalidomide, such measures will appear from the EU-RMP. Examples of risk reduction measures include special written patient information, limited pack sizes, guidance for healthcare professionals.¹⁴ All EU-RMPs must be approved by the authorities, and *EU-RMPs with risk reduction measures* are published (Appendix 1). The working group has decided to exclude these medicines as they are not comprised by the definition of *medicines most frequently involved in serious adverse drug events*. The manufacturer assesses that the handling of the medicine poses a potential risk of causing an adverse event. The working group has compared the list of *EU-RMPs with risk-reduction measures* (Appendix 1) with the list of *medicines most frequently involved in serious adverse drug events*. Both lists contain the same medicine groups, but the lists do not currently share any specific active substances.

Certain medicines are only associated with a risk for special patient groups. Examples of risk patients include children, pregnant women, elderly patients, patients suffering from dementia or patients with renal impairment. The information about risk patients are most frequently based on empirical results from the development of the medicines, for example, from studies of the pharmacokinetics of the medicines. Knowledge about risk patients will be included in the Danish Medicines Agency’s summary of product characteristics, stating contraindications for use in special patient groups.

The working group has not included medicines where the risk only pertains to ‘prescribing the wrong medicine to a known risk patient’ described in the summary of product characteristics and where no known serious pADEs exist. The working group has, however, decided to include medicines for which it has been documented that, for example, lack of dosage adjustment for a special patient group has caused serious ADEs that could otherwise have been prevented.

Data from the Drug Interaction Database¹⁶ are not included as it was not possible for the working group to categorise the interactions as regards serious patient injury. The Drug Interaction Database is developed based on scientific articles on observed interactions – theoretical interactions are not included. The Drug Interaction Database categorises interactions between two active substances in three levels based on the information stated in the articles, the most serious type being designated ‘the combination should be avoided’. As of September 2010, 106 ‘the combination should be avoided’ interactions were found. One of the criteria for the designation ‘the combination should be avoided’ is that the clinical significance is distinct, i.e. a distinct clinical/physiological effect with either significant changed therapeutic response (quantitatively and/or qualitatively) or frequent occurrence of serious adverse drug reactions, in particular if it is not possible to avoid the interaction by dosage adjustment (e.g. because of large individual variation), or there is poorly documented effect of one or both substances (e.g. the interaction between cranberries and warfarin). If equal alternatives exist to one or both of the substances, the interaction is also categorised as ‘the combination should be avoided’. There is thus no clear relation between the severity of any injury and the designation ‘the combination should be avoided’.

Excluded medicines

When reviewing the adverse events, some medicines were excluded from the list of *medicines most frequently involved in serious adverse drug events*. Reasons for exclusion:

- 1 No marketing authorisation in Denmark (colchicine).
- 2 Inadequate description of adverse event. The medicine was involved in an event (DPSD SAC score 3 event and descriptive epidemiological study), but, in the opinion of the working group, the description of the event was not sufficiently detailed to be able to assess the course of events in question as regards injury and/or preventability (lithium, paracetamol, ACE inhibitors and angiotensin II antagonists)
- 3 Interaction. The medicine was involved in an event (DPSD SAC score 3 event and descriptive epidemiological study) which the working group, following an assessment, decided not to include in the list as interaction was mentioned in the event description (metformin and the x-ray contrast agent iodine).

Preparation of the list

Based on the definition, active substances and medicine groups were identified, where errors have led to health consequences, such as hospitalisation, prolonged hospitalisation, permanent injury or death. The identification was carried out by reviewing the literature and cases from the DPSD and the Danish National Agency for Patients’ Rights and Complaints.

The working group has conducted an assessment of the sources and has, in its identification of medicines, focused on those posing a documented and clinically significant risk.

The medicines were described using the variables listed in Table 3.

Table 3. Description of variables for preparing a Danish list of medicines most frequently involved in serious adverse drug events

Variable	Description of variables and associated categories for classifying the list of medicines most frequently involved in serious adverse drug events
Active substance:	Generic name
Sector:	Primary (1) or secondary sector (2). Nursing home is stated in parenthesis after primary sector.
ATC code:	Specification of as detailed ATC code as possible for the active substance in question or medicine group.
Medication process stage:	Documentation for at which stage in the medication process the error occurred (prescription, dispensing, administration, monitoring, compliance).
Error type:	Which type of error has occurred (increased risk of adverse event due to the pharmacology of the medicine, medication process errors or patient errors). If possible, it is also specified if this has resulted in a risk of dosage errors or administration of the wrong medicine.
Error description:	Description of the error causing the event.
Clinical consequence:	Description of which physiological injury the adverse event caused for the patient.
Factual consequence:	Description of how the event has affected the patient’s health condition (hospitalisation, prolonged hospitalisation, necessary life-saving treatment, permanent injury or death).
Documentation:	Source type (case report or epidemiological study).

Source:	Reference for the information.

Sources

Epidemiological studies

A review was made of systematic survey articles and descriptive epidemiological studies concerning the primary (general practice and nursing homes) and secondary sectors, respectively. These studies are reviewed in Appendix 3. The studies show large differences as regards calculation methods and are thus difficult to compare.

In general practice, 67 pADEs are expected per 1,000 patients per year. In nursing homes, 83 pADEs are expected per 1,000 residents per year (Appendix 3). These expectations are based on observations.

The following medicine groups were associated with the highest incidence of pADEs in general practice requiring hospitalisation:

- Cardiovascular drugs (47 % hospital admissions due to pADEs)
- Drugs acting on the central nervous system (15 % hospital admissions due to pADEs)
- Drugs acting on the respiratory system (12 % hospital admissions due to pADEs)
- Analgesics (12 % hospital admissions due to pADEs)
- Antibiotics (10 % hospital admissions due to pADEs)
- Hypoglycaemics (sulfonylurea and insulin) (8 % hospital admissions due to pADEs)

Apart from oral contraceptives and first-generation antihistamines, which are only reported in studies from the 1970s, the same medicine groups have in general practice been involved in adverse events over time.

In nine studies from the secondary sector, the incidence of lethal ADEs was 0.009 - 0.6% for hospitalisations, patients or medicine prescriptions.

The majority of the deaths in the secondary sector could be related to the following medicine groups:

- Anticoagulants (warfarin, heparins)
- Opioids
- Antidiabetics (insulin and oral antidiabetics)
- Antibiotics
- Digoxin

These medicine groups correspond to those found in national reporting systems in the UK and Denmark (Appendix 3).

Databases and other published case reports

The point of departure for Danish studies of medication errors¹⁷ has typically been to describe the incidence of errors in the entire medication process¹⁸, specific parts of the medication process, e.g., dispensing^{19, 20} or sector shifts^{21, 22, 23} or a specific problem, e.g. mix-ups²⁴ or the use of medicine adjustment²⁵. The studies only describe the medicines involved to a limited extent. A systematic review of 811 prescription errors in Denmark from 2008 describes that the 18 most serious errors can be related to very few medicines, with insulin, warfarin, morphine and anaesthetics each involving more than one pADE²⁶.

The National Board of Health’s DPSD database of AEs categorises the reports, and it has been possible to find all AEs caused by medication errors and with a factual SAC score 3 with a view to a discussion in the working group. In its theme report on high-risk medicines from 2007⁵, the National Board of Health has previously described 26 factual AEs with SAC score 3. These include ADEs with the following groups: Antibiotics, anticoagulants, antihypertensives, analgesics, antidiabetics and cytostatics⁵. For each medicine group, 2-4 serious ADES have been reported. In the UK, a similar list was prepared with the medicine groups most frequently involved in serious ADEs in 2007 (updated in 2009)⁴, listing the same medicine groups as the Danish theme report, but the medicine groups anaesthetics, opioids and cardiovascular drugs have been added to the list⁴.

In addition, the working group systematically searched in the database of the Danish National Agency for Patients’ Rights and Complaints in 2009, as well as, published cases involving serious pADEs from this year include insulin, potassium, digoxin, adrenalin, methotrexate, NSAIDs, morphine, phenobarbital and warfarin²⁷.

Pro.Medicin.dk (Infomatum A/S) has prepared patient safety information for specific medicines to assist healthcare professionals in connection with the prescription and dispensing of medicine. The decision as to which medicines are provided with patient safety information is mainly based on knowledge from the DPSD and the Danish National Agency for Patients’ Rights and Complaints. In 2010, 136 products distributed between 14 active substances/medicine groups were provided with a patient safety text²⁸.

In a folder on appropriate polypharmacy (‘Hensigtsmæssig polyfarmaci –en værktøjskasse’), Central Denmark Region has published a top 10 of medicines resulting in hospitalisation²⁹. This list includes NSAIDs, diuretics, warfarin/acetylsalicylic acid, ACE inhibitors, antidepressants, beta blocking agents, opioids, digoxin, prednisolone and clopidogrel. The choice of these specific medicines is based on information from an article in the British Medical Journal from 2004³⁰.

The above information has been included in the preparation of the proposed list of *medicines most frequently involved in serious adverse drug events*.

List of medicines most frequently involved in serious adverse drug events

The process of identifying candidates has resulted in two lists of *medicines most frequently involved in serious adverse drug events*: a list of active substances (Table 5) and a list of medicine groups (Table 6). It has not been possible in all instances to extract specific active substances from systematic survey articles, and the working group has thus decided to include the identified medicine groups. The lists in Tables 5 and 6 are in alphabetical order.

The working group’s actual product – the all-inclusive list of *medicines most frequently involved in serious adverse drug events* – is presented in Appendix 4 in the form of a spreadsheet. The working group expects that users of the list will adjust it as regards, e.g., sector, consumption of specific medicines and high-risk situations.

Table 5. High-risk situation active substances listed in alphabetical order (the pharmaceutical form is mentioned if relevant).

Active substances

Acetylcysteine, concentrate for solutions for infusion ⁵

Amiodarone ^{5, 27}

Digoxin ^{5, 27, 30, 49, 53, 70, 72, 75, 77, 81, 91, 93, 94}

Epinephrine (adrenaline) ^{27, 69}

Ferri-salts, injection fluid ⁶⁹

Fosphenytoin ⁵

Glucose ^{5, 68, 69}

Glyceryl trinitrate ⁵

Lidocaine ⁵⁴

Levothyroxine ⁶⁸

Methadone ^{5, 68}

Metoprolol ^{5, 30, 79}

Nifedipine ⁴²

Norepinephrine (noradrenaline) ^{5, 69}

Phenobarbital ^{27, 69}

'High-alert medicines' working group 2008-10

Phosphate, concentrate for solution for infusion ⁵
Phytomenadione (Vitamin K ₁) ⁶⁹
Potassium, mixture and concentrate for solution for infusion ^{27, 42, 69}
Prednisolone ^{30, 73, 74}
Propofol ⁶⁹
Sodium polystyrene sulfonate ⁴²
Suxamethonium ¹⁰¹
Thiopental ⁵

Table 6. High-risk situation medicine groups listed in alphabetical order. If the specific active substance is known, such substances will be mentioned.

Medicine groups (specific active substances and subgroups)
Antibiotics (amoxicillin, ceftriaxone, cefuroxime, ciprofloxacin, gentamicin, nevirapine, penicillin) ^{5, 42, 50, 53, 68, 69, 79, 82, 93, 99, 100}
Antidepressants (SSRI) ^{96, 97, 98}
Antipsychotics (haloperidol, quetiapine, zuclopenthixol) ^{5, 42, 53, 68, 73, 86, 95, 96, 97, 102, 103, 104, 105}
Antithrombotics and coagulation inhibitors (acetylsalicylic acid ^a , clopidogrel, enoxaparin, phenprocoumon, tinzaparin and warfarin) ^{5, 27, 30, 42, 51, 52, 53, 68, 69, 72, 73, 74, 75, 77, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92}
Benzodiazepines (midazolam, triazolam) ^{42, 53, 68, 78, 79, 80, 85, 88, 96, 97}
Cytostatics (carboplatin, daunorubicin, etoposide, 5-fluorouracil, methotrexate) ^{5, 27, 42, 68, 69}
Diuretics (furosemide, thiazide diuretics ^a) ^{5, 53, 70, 71, 72, 73, 74, 78, 81, 82, 84, 85, 86, 92, 95, 96, 97, 98}
Insulin ^{5, 27, 42, 53, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79}
NSAIDs ^{27, 53, 54, 72, 73, 74, 82, 91}
Strong opioids (morphine, oxycodone) ^{5, 27, 50, 51, 54, 68, 69, 73, 78, 80, 90}

^a Mainly related to dose for elderly people.

High-risk situations and medicines

The review of adverse events has shown that there is a close relationship between the involved medicines and specific situations during the handling of the medicine. It is often not the medicine itself that poses a risk but the context in which it is used, i.e. linking the medicine to the process for the specific situation in which an adverse event has occurred. By identifying where in the medication process the risk of errors occurs, it will be possible to target interventions aimed at specific types of errors and risk situations (Table 7). The spreadsheet accompanying the report shows significant high-risk situations identified in the material.

Table 7. Examples of ADEs and consequences of medicines most frequently involved in serious adverse drug events listed in alphabetical order

Active substance/ group	ATC code	ADE	Therapeutic consequence
Amiodarone	C01BD01	Misadjustment of drip counter.	Life-saving treatment due to bradycardia caused by overdosage.
Carboplatin	L01XA02	Full dose prescribed disregarding white blood cell count.	Hospitalisation due to sepsis caused by overdosage.
Digoxin	C01AA05	Lack of monitoring of serum digoxin. Choice of wrong dose in electronic medicine module.	Hospitalisation, prolonged hospitalisation, life-saving treatment or death due to arrhythmia caused by overdosage.
Enoxaparin	B01AB05	Lack of prescription, lack of discontinuation after a fall.	Hospitalisation or permanent injuries or death caused by a blood clot or bleeding.
Epinephrine (adrenaline)	C01CA24	Mix-up of products, lidocaine and epinephrine as well as heparin and epinephrine , respectively.	Life-saving treatment due to cardiac arrest.
Ferric salts	B03AC02	Higher than prescribed dose dispensed because of failure to notice strength of medicine.	Prolonged hospitalisation due to toxic reaction.
Fosphenytoin	N03AB05	Infusion of bolus dose at high rate for long period of time.	Life-saving treatment due to cardiac arrest.
Glucose		Medicine mix-up, sodium chloride and glucose; increased infusion rate.	Prolonged hospitalisation or life-saving treatment due to hyperglycaemia, hypoglycaemia or cardiac arrest.
Glyceryl nitrate	C01DA02	Misadjustment of infusion rate caused overdosage.	Life-saving treatment due to cardiac arrest.

‘High-alert medicines’ working group 2008-10

Active substance/ group	ATC code	Medication error	Therapeutic consequence
Insulin	A10BA01	Lack of blood glucose measurement; lack of coordination between glucose and insulin drip; mix-up of insulin products.	Hospitalisation or prolonged hospitalisation due to hypoglycaemia or hyperglycaemia.
Lidocaine	C01BB01	Wrong dose administered.	Life-saving treatment due to bradycardia.
Methotrexate	L01BA01	Mixing up daily dose with weekly dose in connection with prescription or dispensing; too high dose prescribed; full dose prescribed disregarding white blood cell count.	Hospitalisation or prolonged hospitalisation due to severe immunosuppression.
Metoprolol	C07AB02	Too rapid dose increase.	Prolonged hospitalisation due to bradycardia and hypotension.
Morphine	N02AA01	Lack of conversion (direct translation of mg to ml where the strength was 10 mg/ml); lack of dose reduction for elderly patients.	Life-saving treatment due to impaired consciousness.
Nifedipine	C08CA05	Administration of wrong dose; incorrect instruction about dosage quantity.	Hospitalisation due to hypotension.
Norepinephrine (noradrenaline)	C01CA03	Unintentional closing of pump and three-way valve, respectively, resulting in underdosage.	Life-saving treatment due to risk of cardiac arrest.
NSAID	M01A	Lack of attention in connection with prescription (too high dose prescribed or prescription to patients with history of ulcers).	Hospitalisation and permanent injuries due to ulcer.
Penicillin	J01C	Mix-up of units (mg and million units) and too late dispensing of medicine.	Prolonged hospitalisation due to liver damage and respiratory failure.
Potassium	B05BB02	Lack of dose reduction; stronger than prescribed concentration dispensed; dose administered intravenously instead of orally.	Life-saving treatment due to severe hyperkalaemia.
Tinzaparin	B01AB10	Not prescribed after surgery or after discharge; lack of administration; lack of	Hospitalisation or permanent injuries due to pulmonary embolism.

		monitoring of INR level.	
Warfarin	B01AA03	Lack of monitoring of INR level; lack of response to increased INR level.	Hospitalisation or death due to bleeding due to increased INR level or blood clots due to too low INR level.

For future updating of the list, the working group suggests that the specific *medicines most frequently involved in serious adverse drug events* be linked with the identified high-risk situations and sector.

Discussion

The working group has fulfilled the terms of reference by preparing a proposal for a national definition of and listed a number of *medicines most frequently involved in serious adverse drug events* based on knowledge from literature studies and reporting sources, respectively – the Danish Patient Safety Database and the Danish National Agency for Patients’ Rights and Complaints.

The working group has discussed the term ‘high-risk medicines’ (‘risikolægemedler’ in Danish) in detail, as the term ‘risk’ is normally associated with the possibility of making quantitative comparisons. The working group has noted that other countries working with reporting systems for pADEs have had similar discussions and that they have made different terminological choices – ‘high-risk medication’, ‘high-alert medication’ or sometimes no designation at all. The working group has decided on a pragmatic solution focusing on the interplay between the two factors, the medicine and the situation, and this has resulted in the introduction of the term ‘*medicines most frequently involved in serious adverse drug events*’ (‘risikosituationslægemedler’ in Danish).

The sources of knowledge for *medicines most frequently involved in serious adverse drug events* have varied considerably and the documentation specified thus also differs as regards level. However, the working group still found a high degree of agreement between the different sources of knowledge for *medicines most frequently involved in serious adverse drug events*. As regards the primary sector, the sources have mainly been systematic survey articles and descriptive, epidemiological studies with very little knowledge of specific cases. As regards the secondary sector, the sources have mainly been cases from reporting systems and the Danish Patient Safety Database and the Danish National Agency for Patients’ Rights and Complaints which do not contain systematically gathered data. The working group has decided to include both source types in its background material. In preparing the report, the working group placed considerable emphasis on ensuring that the following two factors were present in the material: 1) documentation for injury and 2) the description of the specific event. Against this background, the working group has assessed whether the event made the medicine involved relevant for being selected as a *medicines most frequently involved in serious adverse drug events*. In this way, the working group’s product differs from the US list from the ISMP which, as far as we can see, has used a consensus process without taking into account specific examples to decide on what *medicines most frequently involved in serious adverse drug events* are. For future updating of the list of *medicines most frequently involved in serious adverse drug events*, there will also be access to specific cases from the primary sector as the Danish Patient Safety Database was extended to also cover this section as of 1

September 2010.

It appears from the data sources that there are multiple occurrences of the same medicine in both event reports and in the literature. The epidemiological studies have also shown that the medicines for the list of *medicines most frequently involved in serious adverse drug events* correspond to those dating back to as early as the 1970s – with the exception of contraceptives and antihistamines. The working group has thus found that there is considerable knowledge about risks – even though it has not been possible to obtain valid data about the frequency of events in relation to consumption.

On the one hand, the working group has focused on keeping the list short while, on the other hand, focusing more on specific medicines and associated specific challenges and less so on medicine groups, as the list of medicine groups may easily include all medicines. Therefore, the working group has excluded some medicine groups mentioned by the NPSA and the ISMP.

To better illustrate the problems associated with the *medicines most frequently involved in serious adverse drug events* for the users of the list, the working group has prepared tables with examples describing details of the situations in which the events occurred (at which point of the medication process they occurred – as well as the characteristics of the event situations). International lists of *medicines most frequently involved in serious adverse drug events* do, to a certain extent, also include similar tables. In these lists, the tables have been accompanied by initiatives aimed at improving patient safety. The documentation for the proposed initiatives are generally very limited, and the working group has thus decided not to provide proposals for how those involved in the practical work in the health sector should handle risks.

Proposals

The definition and list of *medicines most frequently involved in serious adverse drug events* are intended for those involved in the practical work in the health sector as basis for their own work with risks related to the medication process. In this context, the list should be seen as an all-inclusive list which must be related to local event patterns and medicine consumption.

In addition, the working group proposes a number of potential initiatives at national level which can improve the monitoring of the risks identified as well as limit the occurrence of new risks:

1. Better registration of serious medication errors for learning purposes

The working group recommends that a common national classification of medication errors be prepared and that a shared (anonymised) database containing events from both the Danish National Agency for Patients’ Rights and Complaints (DPSD) and the Danish Patient Insurance Association be established. This will increase the opportunity to monitor *medicines most frequently involved in serious adverse drug events* and high-risk situations and may thus contribute to targeting patient safety initiatives.

2. Ongoing identification of potential *medicines most frequently involved in serious adverse drug events*

The working group recommends that the proposed list be regularly updated through screening of data from the DPSD, the Danish National Agency for Patients’ Rights and Complaints, the Danish Patient Insurance Association, the Danish Medicines Agency’s Pharmacovigilance and published literature.

3. Dissemination of the list of *medicines most frequently involved in serious adverse drug events*

The working group finds that the list of *medicines most frequently involved in serious adverse drug events* should be included in both both pre and postgraduate training of healthcare professionals in the form of specific teaching material. It is proposed that this teaching material be integrated in pharmacology training courses. The working group recommends that a campaign on *medicines most frequently involved in serious adverse drug events* be launched and that the report and the list be translated into English and launched on a European level to other medicines agencies and patient safety organisations.

4. *Medicines most frequently involved in serious adverse drug events* committee

The working group recommends that a permanently anchored committee be established with the responsibility of updating the proposed list of *medicines most frequently involved in serious adverse drug events* (described under item 2) as well as for developing specific information material to reach the target groups (described under item 3). This committee will also be able to contribute to preparing an error and injury classification (described under item 1).

The proposals will hopefully be translated into initiatives for improving patient safety. The working group sees the report as the first phase of a process to be followed up by different preventive initiatives. To this end, projects will be required to document that specific changes in the handling of medicines improve patient safety.

List of definitions

Adverse drug reaction (ADR): A harmful and unintended reaction that occurs at a medicine dose normally used for humans or animals for the prophylaxis, diagnosis or treatment of disease or to modify, regenerate or correct physiological function^{31, 10}.

Adverse event (AE): An adverse event is an event occurring in connection with healthcare activities, including prehospital efforts or in connection with the supply of and information about medicines.

Adverse events include events and errors known in advance and unknown events and errors not caused by the patient’s disease and which are either harmful or could have been harmful but which were prevented before occurring or which did not otherwise occur due to other circumstances⁴⁰.

This definition used in Denmark also includes medication errors which could be potentially harmful had they not been prevented. Other definitions of the concept only include the factual AEs. The working group has chosen this definition as it is legally applicable in the area, and which, amongst others, risk managers follow. In relation to the above definition, the working group has dealt with factual harmful AEs.

The underlying terms for adverse event are defined as follows:

Adverse drug event (ADE):
Harmful event caused by a medicine and not caused by the patient’s underlying disease^{34, 10}.

Preventable ADE (pADE):
Event that could have been avoided by better use of available knowledge and technology³³.

Non-preventable ADE:
An event where injury could not have been prevented in the specific situation in spite of correct use of available knowledge and technology³³.

See the clarification of the concept of adverse events in Appendix 5.

Case report:	In medical science, a published description of a single case, detailing, e.g., unusual symptoms ³⁵ . In this report, case reports included spontaneous reports from the DPSD (SAC 3 score) as well as complaints and cases concerning damages from the Danish National Agency for Patients’ Rights and Complaints.
Compliance:	Expression of the patient’s ability and/or willingness to follow a given prescription ³² .
Error:	Event leading to an unintended result, but which could have been prevented ¹ . Errors include both <u>active errors</u> (errors resulting from an action actively performed by a person with direct patient contact ³³ , e.g. omissions, mistakes and/or intentional or unintentional non-compliance with rules) and <u>latent errors</u> (possibility of error conditional upon the structure of the organisation, training procedures, maintenance of equipment etc. ³⁴ The errors may be dormant for a long period of time ¹⁰).
Healthcare professionals:	Persons authorised in accordance with special legislation to perform healthcare tasks, and persons whose actions are the responsibility of those authorised ³⁸ .
Inappropriate medication use:	Medicine consumption where the negative effects overshadow the positive effects ³⁹ .
Interaction:	Change in the effect of a medicine caused by concomitant administration of another medicine. Interactions include synergism, where two substances reinforce the effect of each other, or antagonism, where two substances mutually neutralise the effect of each other or one neutralises the effect of the other. Interactions may also be caused by inhibition, where the metabolism of a medicine is inhibited by concomitant administration of another medicine, or by induction, which means increased metabolism of a medicine by concomitant repeated administration of another medicine. Interactions may also occur between medicines and food which may reduce the absorption and thus the effect of the medicine ³² .
Look-alike (visual mix-up):	Mixing up medicine names when reading.
Medication error:	An error occurring during the stages of the medication process – prescription, dispensing, administration and monitoring of the effect –

causing injury or involving a risk of patient injury^{36, 10}.

Near-incident:

Errors corrected in time before the action is completed³³.

Pharmacovigilance:

The science and activities relating to the identification, assessment, understanding and prevention of the adverse effects of pharmaceutical products¹⁰.

Risk management plan:

The marketing authorisation holder (MAH) must complete a risk management plan for each new medicine or when updating an existing medicine on the market. The risk management plan consists of:

- A safety specification
- A pharmacovigilance plan
- An assessment of the need for risk reduction measures
 - If required, the MAH must have a plan for risk reduction measures

The risk management plan, including the plan for risk reduction measures, must be approved by the Danish Medicines Agency before the medicine is marketed^{14, 15}.

SAC score:

Safety Assessment Code.

Classification system for the severity of adverse events in the DPSD. The risk score is calculated based on the severity degree (extent of injury) and the frequency of the event (probability of repetition). The SAC score is divided into level 1, 2 and 3, with 3 being defined as a catastrophic injury or a frequently occurring injury of significance to the patient³⁷.

A distinction is made between a factual SAC score and a potential SAC score. A potential SAC score is an expression of the injury which could have occurred had the event not been stopped. A factual score is an expression of the injury actually caused by the event.

**Sound-alike
(auditive mix-up):**

Mixing up medicine names when pronounced.

(Treatment) injury:

Inappropriate consequence of treatment performed according to good medical treatment practice. Causing either temporary or permanent injuries.

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Appendix 1 Medicines with a risk management plan with special conditions (20 September 2010)

The approval of the medicines listed below, i.e. the registration or updating of the marketing authorisation, involves a risk management plan which contains special measures (conditions) that must be implemented to ensure safe and effective use of the medicine.

The individual risk management plans can be viewed by clicking the names of the medicines, including the measures to be implemented and the party responsible for this.

Name of medicine	Marketing authorisation holder	ATC code
Drugs with Isotretinoin (see item 4.4)	Sandoz etc.	D10BA01
Aclasta®	Novartis	M05BA08
Benefix®	Wyeth	B02BD04
Brinavess®	Merck & Dohme Ltd. UK	C01BG11
Cimzia®	UCB Pharma SA	L04AB05
Daxas®	Nycomed GmbH, Konstanz, Germany	R03DX07
Efient®	Eli Lilly Netherland B.V	B01AC
Exjade®	Novartis	V03AC03
Gliolan®	Medac	L01XD04
Ilaris®	Novartis Europharm Ltd., GB-Horsham, West Sussex, UK	L04AC08
Increlex®	Tercica Europe Limited. Ireland	H01AC03
Instanyl®	Nycomed Danmark ApS	N02AB03
Kaletra®	Abbott	J05AEA06
Lucentis®	Novartis	S01LA04
MabCampath®	Genzyme	L01XC04
Macugen®	Pfizer	S01LA03
Mircera®	Roche	B03XA03
Multaq®	Sanofi-Aventis, Paris, France	C01BD
Mycamine®	Astellas Pharma Europe B.V.	J02AX05
Nplate®	Amgen Europe BV	B02BX04
Qutenza®	Astellas Pharma Europe B.V.	N01BX04
Renvela®	Genzyme Europe B.V., DC Naarden, Netherlands (11623)	V03AE02
Retacrit®	Hospira Enterprises B.V.	B03XA01
Revlimid®	Celgene	L04AX04
Revolade®	GlaxoSmithKline Trading Services Limited. Ireland	B02BX05
Simponi®	Centocor B.V., Leiden, Netherlands (230800)	L04AB06
Soliris®	Alexion	L04AA23
Stelara®	Janssen Cilag International NV	L04AC05
Tasigna®	Novartis	L01XE08

‘High-alert medicines’ working group 2008-10

Thalidomide Pharmion®	Pharmion Ltd	L04AX02
Thelin®	Encusive	C02KX03
Tracleer®	Actelion	C02KX01
Tysabri®	Elan	L04AA23
Valdoxan®	Les Laboratoires Servier	N06AX22
Volibris®	Glaxo Group Ltd	C02KX02
Zypadhera®	Eli Lilly Netherland B.V. Netherlands	N05AH03

The Danish Medicines Agency will as soon as possible publish further information about risk management plans.

Danish Medicines Agency, last updated on 20 September 2010⁴¹.

Appendix 2 Severity of adverse drug events

The designation of specific medicines as *medicines most frequently involved in serious adverse drug events* must be based on an assessment of the severity of the patient injury caused by factual events and/or a risk assessment of near-incidents or risks detected, e.g. when reviewing medical records.

In the literature, different classification systems are used to assess patient injuries as well as risks. In Denmark, researchers have assessed severity by means of one of the four following methods:

- 1 SAC score severity in the DPSD-1 (divided into four categories) for describing factual events. The following terms are used: minor, moderate, major and catastrophic (Table 8)⁴². At the end of 2010, this scale was replaced by a new scale with the terms: no injury (1), minor (2), moderate (3), serious (4) and death (5) (Table 9)⁴³.
- 2 David Bates’ scale (divided into four categories) for describing potential severity^{44, 45}. The scale uses the terms ‘potentially major’, ‘major’, ‘serious’ and ‘catastrophic’ for scoring (Table 10).
- 3 Foss’ scale (two categories) for assessing potential severity uses the terms ‘clinically significant’ or ‘clinically not significant’²².
- 4 A third method does not base its categorisation on severity but solely on the description of the individual events^{21, 46}.

It should be noted that there is a significant difference in how the term ‘major’ is used in the DPSD SAC score and in David Bates’ classification, and the group in need of acute life-saving treatment is classified differently in the two systems.

In the Danish scientific articles, severity has mainly been assessed by consensus between two persons’ individual scoring or consensus within a team of clinicians. There was moderate agreement between two persons’ individual scoring of descriptions of factual events (kappa value = 0.582 ± 0.034)⁴⁶.

Table 8. Criteria for assessment of factual severity in the SAC scoring system used by Andersen ML et al.⁴⁶, Nielsen RH et al.²⁴.

Factual SAC score severity	Designation
No injury	Minor
Slightly increased need for assessment and treatment – may be handled at the same department and without prolonged hospitalisation	Moderate
Prolonged hospitalisation or hospitalisation from the primary sector or transferral to department with increased level of observation	Major
Acute life-saving treatment	Major
Permanent injuries	Catastrophic
Death	Catastrophic

Table 9. Criteria for assessment of severity in DPSD-2⁴³.

Severity	Designation
No injury.	None (level 1)
Slight temporary injury not requiring increased level of treatment or increased level of care	Minor (level 2)
Temporary injury requiring hospitalisation or treatment by general practitioner or increased level of care or, for hospitalised patients, increased level of treatment.	Moderate (level 3)
Permanent injury requiring hospitalisation or treatment by general practitioner or increased level of care or, for hospitalised patients, increased level of treatment or other injuries requiring acute life-saving treatment.	Serious (level 4)
Death	Death (level 5)

It should, however, be noted that events requiring hospitalisation cannot be delimited independently in the new DPSD-2 database. This will require considerable manual sorting of events scoring ‘moderate’ in the new database.

Table 10. Criteria for assessment of severity in the SAC scoring system used by Lisby M et al.¹⁸ and Larsen MD et al.²³

Designation	Definition	Definition of key terminology
Potentially fatal	Medication error assessed to pose a real clinical risk for the patient’s life	Fatal implies that the medication error could potentially result in the patient’s death
Potentially serious	Medication error assessed to pose a real clinical risk of causing injury to the patient	Injury includes medication errors where it is deemed necessary to initiate active treatment to restore the patient’s health. A serious potential error may cause either temporary or permanent injury to the patient
Potentially significant	Medication errors assessed to pose a real clinical risk of being an inconvenience to the patient without causing injury	Inconvenience includes discomfort due to wrong dose, wrong medicine or lack of dosage of a medicine which may have caused the patient pain, dizziness etc.

‘High-alert medicines’ working group 2008-10

		Measures which would be initiated to monitor the consequences of a medication error, e.g. blood samples, frequent blood pressure measurements etc.
Potentially non-significant	Medication errors assessed to be of no clinical significance to the patient	No clinical reference implies that the patient has been exposed to a medication error, but that the error did not give cause to any injury or unnecessary inconvenience to the patient.

In the scientific literature on events, different classification methods are used to describe the severity of consequences of events and risks. A common characteristic of the severity assessment methods is that they make a clear distinction between less serious events and events/risks causing hospitalisation, prolonged hospitalisation, need of acute life-saving treatment, need of transferral to more intensive monitoring, permanent injury and death.

Appendix 3 Literature review

The review of epidemiological studies concerning the primary (general practice and nursing homes) and secondary sectors was based on existing literature (both Danish and foreign) on medication errors and adverse drug events. The selection criterion for including articles in this report was a description of an ADE with injury. The results are based on literature published up until 2008 (Table 11).

Table 11. List of search results

Sector	Databases	Search terms	Number of studies selected
General practice	PubMed, International pharmaceutical abstracts, Cochrane database of systematic reviews, EMBASE, Web of Science	Medication error, adverse drug reaction, drug therapy/adverse effects, iatrogenic disease/drug therapy AND outpatients, ambulatory care, patient admission, primary medical care	29
Nursing homes	Medline, International pharmaceutical abstracts	Adverse drug events, adverse drug reactions, adverse drug withdrawal events, aged, drug therapy, drug-related problems, medication-related problems, nursing homes, therapeutic failures, treatment failures	7
Secondary sector	PubMed, Cinahl, EMBASE, PsychINFO	Adverse drug event, ADE, ADE/medication errors, ADE/errors	31

In *general practice*, primarily three medicine groups are mentioned (cardiovascular drugs, analgesics and hypoglycaemics) as the cause of 86.5% of all preventable adverse drug events (Table 12)⁴⁷.

Apart from oral contraceptives and first-generation antihistamines, which are only reported in studies from the 1970s, the same medicine groups have in general practice been involved in adverse events over time.

Table 12. Medicines involved in adverse events in general practice⁴⁷.

Medicine group	Adverse drug events (preventable and non-preventable)	Preventable adverse drug events (pADEs)	Fatal and life-threatening (requiring hospitalisation) pADEs
Cardiovascular	33.3% [1.1-73.6%]	47.0% [35.0-59.0%] -	46.6% [6.0-80.0%]
Oral contraceptives	22.5% [19.1-25.8%]	-	-
Drugs acting on the central nervous system	10.1% [6.9-49.7%]	5.3% [0-10.5%]	14.9% [5.0-44.0%]
Drugs acting on the respiratory system	5.6% [0.8-7.8%]	1.0% [1 study]	12.2% [5.3%-14.0%]
Hypoglycaemics (sulfonylurea, insulin)	7.3% [1.3-7.7%]	10.9% [1 study]	8.4% [5.3-16.7%]
Analgesics	9.1% [4.5-22.2%]	28.6% [22.1-35.0%]	11.9% [6.7%-33.3%]
Antibiotics	9.0% [4.0-31.1%]	4.1% [3.1-5.0%]	9.5% [3.3-20.0%]

The percentage specifies the number of AEs, pADEs or serious pADEs, respectively, within each medicine group in relation to the total number of AEs, pADEs or serious pADEs, respectively. Data are presented as median value with corresponding range.

The incidence of adverse events in the primary sector is relatively high, and it is higher at nursing homes than in general practice. The incidence of preventable adverse drug events is of the same order in general practice and at nursing homes, but the proportion of preventable adverse events is twice as high among nursing home residents (Tables 13 and 14). In general practice, it can also be seen that preventable adverse events require hospitalisation to a much larger extent than adverse events in general (Table 13)^{47, 48}.

Table 13. Incidence of adverse drug events in general practice^{a 47}

Incidence in general practice	Number of adverse events
Number of ADEs per 1,000 person-months:	14.9 (4.0-91.3)
Number of pADEs per 1,000 person-months:	5.6 (1.1-10.1)
Percentage of pADE:	21% (11-38%)
Number of ADEs requiring hospital admission per 1,000 person-months:	0.45 (0.10-13.1)
Number of pADEs requiring hospital admission per 1,000 person-months:	4.5 (1 study)

^a Incidence has been calculated per 1,000 person-months to avoid having to extrapolate data beyond the real follow-up time for the individual studies and is presented as median value with corresponding range.

Table 14. Incidence of adverse drug events at nursing homes^{a 48}

Incidence at nursing homes	Number of adverse events
Number of ADEs per 1,000 person-months:	27.0 (11.9-72.6)
Number of pADEs per 1,000 person-months:	6.9 (4.1-9.7)
Percentage of pADEs, that are preventable:	46% (42-51%)

^a Incidence has been calculated in person-months to avoid having to extrapolate data beyond the real real follow-up time for the individual studies and is presented as median value with corresponding range.

Medication errors in the primary sector most frequently occur in connection with prescription and monitoring. More specifically, the most frequent errors are lack of monitoring or lack of response to clinical/laboratory results, patient non-compliance and dosage and frequency errors⁴⁷.

Studies of nursing homes show that cardiovascular drugs are also here involved in most adverse events, followed by drugs acting on the central nervous system, analgesics and antibiotics. Medication errors at nursing homes most frequently occur in connection with prescription and monitoring⁴⁸.

In the *secondary sector*, the medicine groups most frequently involved in adverse drug events are antibiotics, antidiabetics, anticoagulants, antipsychotics, cardiovascular drugs, glucocorticoids, chemotherapy, morphinic analgesics and NSAIDs, diuretics and electrolyte concentrates. A literature review generally shows that pADEs often involve specific processes (referrals, decimal point errors), patient factors (number of medicines, morbidity) and, in particular, specific medicines or medicine groups.

For the *secondary sector*, in eight out of the 33 studies (Table 15) it was possible to identify medicines or medicine groups involved in deaths or life-threatening conditions. Table 15 shows a detailed overview of the incidence of adverse drug events (ADEs), preventable ADEs, fatal and life-threatening ADEs as well as the medicines involved.

‘High-alert medicines’ working group 2008-10

Table 15. Overview of incidence of adverse drug events (ADEs), preventable ADEs, fatal and life-threatening ADEs as well as the involved medicines in the secondary sector.

Medicines involved in fatal or life-threatening ADEs²	ADE n/N (%)	Preventable ADEs n/N (%)	Proportion of fatal or life-threatening ADEs n/N (%)	Reference
Digoxin; antidiabetics (metformin)	235/5,497 (4)	N/A	Death: 5/235 (2)	Raschetti (1999) ⁴⁹
Opioids; antibiotics; analgesics	26/10,778 (0.2)	5/26 (19)	Death: 1/26 (3) Life-threatening: 1/26 (3)	Kaushal (2001) ⁵⁰
Anticoagulants; opioids; insulin; benzodiazepines	2571	317/2,571 (12)	Death: 3/317 (0.9) Life-threatening: 36/317 (11)	Winterstein (2002) ⁵¹
Amoxicillin; acetylsalicylic acid; warfarin; ceftriaxone; midazolam; metoprolol; heparin; insulin	481/6,383 (8)	28/481 (5)	Death: 0 ² Life-threatening: 10/28 (35)	Hardmeier (2004) ⁵²
Warfarin; digoxin; potassium	815 ¹ 9.8/100 months	338/815 (42)	Death: 3/815 (0.4) Life-threatening: 33/815 (4)	Gurwitz (2005) ⁵³
Opioids; lidocaine; combination of NSAIDs and heparin analogues	483/937 (49)	NA	Death: 6/483 (1) Life-threatening: 17/483 (4)	Nebecker (2005) ⁵⁴
Anticoagulants; opioids	1,116 (uni hosp) 4.4/100 hospitalisations 501 (Municipal hosp) 6.2/100 hospitalisations	N/A	Death: 1/1,116 (0.09) Life-threatening: 142/1,116 (13) Death: 3/501(0.6) Life-threatening: 79/501 (16)	Kilbridge (2006) ⁵⁵
NSAIDs, diuretics, warfarin, ACE inhibitors, antidepressants, beta blocking agents, opioids, digoxin, prednisolone	1225/18,820 (7)	Definitely or possibly preventable: Over 70%	Death: 27/18,820 (0.01)	Pirmohamed (2004) ³⁰

N/A: Not Available (information not available)

Appendix 4 All-inclusive list of *medicines most frequently involved in serious adverse drug events*

Separate appendix (spreadsheet) with background material for the list of *medicines most frequently involved in serious adverse drug events*.

Appendix 5 Clarification of the concept of ‘adverse event’ within the pharmaceutical area

The lack of unambiguous concepts is a major problem in the interplay between medicines, patient safety and pharmacovigilance, resulting in inconsistent and incomparable occurrences of medication errors and adverse events related to medicines^{56, 57, 58, 59, 60, 61, 62}. The working group has regularly encountered this problem because the different players have had a fundamentally different perception of the meaning of the concepts:

- Factual **injury** to the patient is a key element of the concept of ‘adverse event’ within pharmacovigilance, whereas risk of injury is sufficient as regards patient safety^{63, 64, 65, 66, 67}.
- **Causal relationship** is central to patient safety where a presumed relationship between an adverse event (AE) and the use or lack of use of a medicine is called an adverse drug event (ADE). Within pharmacovigilance, the concept of ‘adverse drug reaction’ (ADR) is used instead when there is a causal relationship with the medicine^{63, 64, 65, 66, 67}.
- In Danish, ADR is normally translated into ‘bivirkning’ (side effect), and traditionally, as regards adverse drug reactions, it is assumed that the medicine has been **used correctly**. At the same time, a distinction is made between two types in the terminology of adverse drug reactions: Type A reactions which are assumed to be predictable reactions to medicinal treatment. They are often dose-dependent and, to a certain extent, preventable. Type B reactions are most frequently unpredictable^{61, 63, 65, 67}.

Some researchers have also introduced the concept of ‘adverse drug event’ in connection with patient safety, but without a clear division into preventable and non-preventable events.

Other researchers have recently introduced the concept of *adverse events in humans taking medicines*. The concept is divided into:

- 1) an adverse event which is not a reaction to medicinal treatment
- 2) an adverse reaction not caused by an error
- 3) an adverse reaction caused by a medication error
- 4) a harmful medication error not caused by an adverse drug reaction^{56, 58}.

The above concepts all relate to the result for the patient. In comparison, medication errors relate to errors occurring in the process during which the patient is being treated with the medicine. In Denmark, professional experts appointed by 13 healthcare, scientific and professional societies have reached consensus on a definition of medication errors which are defined as errors either causing or having the potential to cause injury to patients. The definition focuses both on the process and drug-related errors, including drug interactions, and has proved reproducible in several clinical studies³⁶. The working group has used this definition of medication errors in the list of definitions in this report.

To the working group, it has been extremely useful that consensus exists on the concept of medication errors and the working group recommends that the relevant parties in Denmark try to reach consensus on the other concepts mentioned which are used in connection with medicines: adverse event

(‘utilsigtet hændelse’), adverse drug event (‘lægemiddelrelateret utilsigtet hændelse’), adverse drug reaction (‘bivirkning’) and preventable adverse drug event (‘forebyggelig lægemiddelrelateret utilsigtet hændelse’) (pADE).

In the report, the working group has decided to take as its point of departure those concepts which originate from patient safety, and the working group agreed to use pADE to the extent possible.

List of abbreviations

DPSD:	Danish Patient Safety Database
EU-RMP:	Risk management plan:
pADE:	Preventable adverse drug event
ISMP:	Institute of Safe Medication Practices
JCAHO:	Joint Commission on Accreditation of Healthcare
ADE:	Adverse drug event
NPSA:	National Patient Safety Agency
NSAID:	Non-steroidal anti-inflammatory drug
USP:	United States Pharmacopeia
AE:	Adverse event