Interaction Database: Description for System Providers

April 2015

Contents

1.0 Introduction

The purpose of the Interaction Database is to g ear treatment with medication more effective and safe. It contains a complete and up-to-date knowledge of the potential undesirable effects of each drug when given in combination.

1.1 About this document

This document is intended as a background material for the system vendors to implement the use of the interaction information in the existing and upcoming IT systems of doctors, pharmacies, hospitals and other places in the healthcare sector or in IT systems aimed at citizens. It thus describes the technical and professional aspects that must be taken into account when using interaction information from the Interaction Database.

1.2 Objective s The

interaction database was established through Project Interaction Database. The purpose was to gather existing available interaction literature and thereby document drug interactions based on the principle of evidence-based drug information. The aim is thus to provide a common frame of reference that can form the basis for the widest possible consensus on the handling of drug interactions in the Danish healthcare system.

1.3 Target audience for the interactioninteraction

information Thedatabase information is formulated for physicians, pharmacists and other healthcare professionals as well as citizens.

1.4 Content of the

interaction database The interaction database describes approx. 4,000 interactions between registered drug substances and selected herbal, food, vitamins and minerals. The description consists of a literature review, a class effect as well as a description of each interaction, its documentation degree and clinical significance, and a recommendation regarding the practical

handling of the interaction. As of July 2011, the Interaction Database has also included herbal and medicinal products reserved for hospital use (SADs).

1.5 Data
The

interaction database is a common platform from which healthcare stakeholders can retrieve data on drug interactions. This data can be retrieved using a web service, such as an XML document containing all available interaction information. Both the XML document (section 4.4) and this web service (section 4.5) are described later in this document. In addition, it is possible to apply the Interaction Database via specific queries to any interactions between single preparations or lists of preparations. For more information, please contact the National Board of Health.

2.0 Project Interaction

Database Project Interaction Database has had four stakeholders:

• The Danish Pharmacists Association (DA)
• Danish Medicines Information A / S (DLI)
• The General Danish Medicines Association (DADL)
• Department of Rational Pharmacotherapy (IRF) The

assessment and description of each interaction was made in collaboration with a scientific scientific committee.

The interaction database has been entrusted to the National Board of Health by the four stakeholders, who will in future take care of the professional maintenance as well as the technical operation and maintenance. The National Board of Health has outsourced the technical operation to KMD and the technical maintenance to Formpipe.

3.0 Interaction Information

3.1 Documentation

Basis More than 12,000 scientific articles have been reviewed and evaluated as the basis for the Interaction Database.

The working method for the construction and maintenance of the database is described in Appendix 2.

3.2 The professional maintenance

The professional maintenance is carried out by the Danish Medicines Agency's Pharmacovigilance & Medical Equipment.

Inquiries regarding professional questions, cf. Appendix 1.
The

National Board of Health has included a professional panel of experts in determining the principles for professional maintenance, cf. Appendix 1.

3.3 Scientific article The

description of each scientific article contains the following data:

• Author (s)

• Journal's journal name, year of publication, volume and page numbers

• Title

• Abstract / Summary

3.4 Definition of interaction

An interaction is described only as a relationship between drug substance and drug substance (ie only between two drugs), since knowledge of interactions between several substances administered simultaneously is sparse or not existing. In addition, descriptions exist between groups of drug substances, called class effect. The grouping is made on the basis of the substances' uniform functioning and / or turnover conditions.

If there are 6 substances in one substance group and 4 substances in another substance group, there is a theoretical possibility of finding 24 different combinations of two arbitrary substances from the two substance groups; in practice, however, it is only possible to find a few of these combinations described in the scientific articles.

The drug-drug-drug combinations are described in the following way, designated “level 3”:

• Degree of documentation - cf.

Appendix 3

• Clinical significance - cf.
Appendix 4

• Conclusion

• Recommendation text

• Recommendation - cf. Appendix
5

• Recommendation Citizen

• Special precautions

• Problems with concomitant use

• NOTE

• Side effect text

The
drug group-drug group combinations are described in the following way, termed “level 2”:

• Literature review

• Class effect

Graphically, the relationship between the two levels can be described as follows:

Figure 1: The relationship between Level 2 and Level 3 for an interaction.

3.5 Example of Interaction

An example of an interaction can be found in Appendix 6

4.0 Data for systems

4.1 Data for systems

The

update application generates an XML file for the web service that is run on the interaction database server. The web service can take this XML file and deliver it to the web service called by the system provider.

Figure 2: System overview

4.2 Release of data

New or updated interaction information is continuously released as it is recorded in the interaction database.

4.3 XML Document
The

description of the DTD and the XSD of the XML documents can be found in Annex 7.1 and Annex 7.2 respectively. A

database diagram showing the relationships between the various tables in the XML document is presented in Appendix 7.3

4.4 Web service

The

interaction database's web service is available at www.pidb.dk/ws/pidbws.asmx.

The description of the web service can be found in
appendix 8.

Appendix 1.
Personnel list

Professional and technical questions can be sent to
interaktion@dkma.dk The

National Board of Health has included medical consultants in determining the principles for professional maintenance:

- Doctor, Ph.D. Hanne Rolighed Christensen, Bispebjerg hospital
- Doctor, Ph.D. Per Damkier, Department of Clinical Pharmacology, Odense University Hospital
- Doctor, associate professor, Ph.D. Birgitte Brock, University of Aarhus

Appendix 2. Basic working method

Appendix 2.1. The build-up

phase 2.1.1
Selection

In order to select the drug interactions to be included, we have examined which interactions are listed in:

• Micromedex (www.smi.dk)

• Hansten (www.drugfacts.com)

• PubMed (http: / /www.ncbi.nlm.nih.gov/PubMed/)

The association amount of interactions described in these 3 sources was listed and they were included in the database.

In addition, the interactions that are described in:

• Product(The National Board of Health)

summaries• Medicin.dk
(Infomatum A / S)

These inclusion criteria were “minimum criteria”, including relevant interactions found in the below searches in PubMed.

2.1.2 Prioritization

The selected interactions were reviewed with a view to prioritizing, as well as making the necessary division of the drug substances into drug groups.

2.1.3 Searching for scientific articles

2.1.4 Review articles for selection

PubMed was also searched for review articles.

2.1.5 Primary Literature for Level 1

After selecting which interactions to investigate with the selected drug substance or drug group, a thorough search of the interaction was performed in the primary literature. Literature is ordered through the Royal Library (dab@dab.dk).

2.1.6 Staffing

The build-up was carried out by 2 pharmacists and a number of specialized specialist consultants, led by project manager Mogens Brandt Kristensen.

Appendix 2.2 Maintenance and update

2.2.1 General principles for included interactions The interaction

database should, as a rule, only be updated if the interaction is:

- Pharmacokinetic, **and**
- Based on human data (studies, case studies)

As a general rule, **NOT**:

- Expected and / or less significant pharmacodynamic interactions, **or**
- Theoretical interactions, **or**
- In-vitro interactions and animal studies

2.2.2 Content and update The

content of the interaction database is updated on the basis of monthly systematic literature searches from the Royal Library. The literature searches are done in the PubMed and Embase databases based on specially defined keywords and search criteria.

The database is updated on an ongoing basis with product summary summaries of new substances.

2.2.3 Staffing

Maintenance and updating of the database is carried out by the professional working group, which consists of 2 academic staff and 2 students.

The working group collaborates with a part-time specialist in clinical pharmacology on the clinical assessment of drug interactions.

Appendix 2.3. Description of the interaction at the individual levels The

interaction database is described at 3 levels.

2.3.1 Level 1

Abstract of found articles in PubMed can be read in the database. The article is evaluated according to a determined method for assessing the design, dose, number of subjects, statistics and relevance; in addition, an assessment and conclusion is made.

2.3.2 Level 2

Overall literature review of the relevant studies described in Level 1 with reference references. The result of a possible interaction is stated as accurately as possible. For example, "when concomitantly administered with drug A and B, the concentration in drug blood A increases an average of 30% (possibly + - SD)". Mechanism of action responsible for any interaction is also described. If there are drug substances in the drug group that are not described in the literature, this is also described by stating that there are no localized studies that describe the effect of drug A on drug B. If there is a theoretical probability of interaction, this is stated below. Literature references in the text are given.

In addition, themust be *class effect* described. Class effect is a description of the interaction for the substance group associated with the individual drug substances described in Level 3.

2.3.3 Level 3

Conclusion on the drug-drug interaction. In the short conclusion, the drugs that interact, indicate the consequence if possible in numbers: "concentration increases ...%". Also, the mechanism of action is indicated, if known. The description of the level 3 interaction is made on the basis of level 1 and level 2 and should be read as a separate text.

In addition, assessment of the degree of *documentation, clinical significance* and *recommendation* and any *recommendation text*.

For the Citizen Edition, *special precautions* and *problems are described* when used concurrently. The field *OBS* can be used in special cases (but this has not happened yet). The health professional *recommendation* is automatically translated into a *recommendation citizen*. In addition, a color and an adverse reaction text are automatically, cf. Appendix 5.

Appendix 3. Degree of

documentation
Thedocumentation

assignedfollowinghave been established:

degrees ofWell-documented: At least 2 (from different centers) human controlled studies and / or (before and after) studies on relevant individuals with single- or multiple-dose (steady-state) trials in the form of either significant kinetic or dynamic changes.

Documented: A human controlled study and / or (before and after) study with single or multiple dose (steady state) studies in the form of either significant kinetic or dynamic changes.

Limited documented: Either more than 2 casuistic messages with relevant before and after kinetics or dynamics.

Poor documented: 1-2 case studies.

Appendix 4. Clinical

implications

Pronounced: Pronounced clinical / physiological efficacy with either significant altered therapeutic response (quantitative and / or qualitative) or frequent occurrence of serious adverse events.

Moderate: Moderate clinical / physiological efficacy with either slightly altered therapeutic response, or rare occurrence of more severe adverse reactions, or frequent occurrence of minor adverse reactions. Serum concentration changes that in other experiments have been closely associated with the above phenomena.

Poor: Unchanged or not significantly altered biological response with few and minor side effects - or serum concentration changes that in other experiments have not shown significant changes in biological response.

Possible: Pharmacokinetic changes that are not accompanied by known side effects or changes in the biological response, or solely results from in vitro studies that cannot be associated with clinical / physiological endpoints.

None: Neither kinetic nor physiological / clinical changes.

Undetermined: Kinetic or physiological / clinical changes that cannot be assessed on the basis of the available documentation.

Appendix 5. Recommendations with related text

The

recommendation is set to one of the six described below.

When selecting recommendation text 3) -5) a text should be added which can guide the clinician. Examples of this can

be seen below.

In recommendation 1) or 6) there is usually nothing in the recommendation text. However, it should be mentioned if the interaction is only seen in a minority.

1 The combination should be avoided.

2 The combination can be used with dose adjustment.

Examples:

- The dose of X should be reduced / increased (by about 1/3, 1/4 electricity)
- Dose increase / reduction of X may be necessary depending on the effect / side effects and / or concentration measurements.

3 The combination can be used with a delayed intake time.

Examples:

- A should be taken X hours before / after B
- A and B should be taken at X hours interval

4 The combination can be used under certain precautions.

Example:

- Frequent control of drug X's effect / side effects on initiation and cessation of combination therapy

5 The combination can be used

Appendix 6 example of Interaction

6.1 Level 2

Substance group nameSubstance

Substancegroup A namesantacid Aluminum, calcium, Cromoglicic acid, magnesium, sodium acetate, sodium alginate, sodium chloride, sodium citrate, sodium dihydrogen

phosphate, sodium edetate, sodium fluoride, sodium salt, natriumhyalorunat, sodium bicarbonate, sodium hydroxide, sodium iodide, sodium lactate, natriumnedocromil, sodium picosulfate, sodium thiosulfate

Substance Group B fluorochinoloner ciprofloxacin, fleroxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin

literature review
norfloxacin

Aluminum and magnesium

Several studies show that the bioavailability of norfloxacin is significantly reduced when norfloxacin is taken concurrently with aluminum and magnesium. Campbell NR, Kara M et al, 1992 show that the bioavailability of norfloxacin decreases with concomitant treatment with aluminum or magnesium, which can be seen by reducing the urinary excretion of 400 mg norfloxacin by 8 subjects by 86% and 90%, respectively. Shiba K, Sakamoto M et al, 1995 show that aluminum administered concomitantly with 200 mg of norfloxacin in 5 healthy subjects reduces the AUC of norfloxacin to less than 30% of the AUC of norfloxacin without concomitant administration of aluminum. Nix DE, Wilton JH et al, 1990 show in a crossover trial of 12 healthy subjects that the relative bioavailability of 400 mg norfloxacin taken 5 min after 30 ml of Maalox (magnesium + aluminum) is 9% compared to 400 mg norfloxacin consumed without Maalox. In addition, the study shows that if Maalox is taken 2 hours after norfloxacin, no significant reduction in the relative bioavailability of norfloxacin is seen. A single case describes that clinical efficacy is reduced when Maalox is taken concomitantly with norfloxacin Noyes M and Polk RE, 1988. Calcium Nix DE, Wilton JH et al, 1990 show that the relative bioavailability of 400 mg norfloxacin taken 5 min after 30 min. per ml calcium calcium is approx. 37% compared to norfloxacin alone.

Ciprofloxacin

Aluminum and Magnesium

The relative bioavailability of ciprofloxacin administered 5-10 minutes, 2 hours or 4 hours after Maalox is significantly reduced by 85%, 77% and 30%, respectively, according to a cross-over study with 12 healthy subjects by Nix DE, Watson WA et al, 1989. The study further shows that ingestion of Maalox either 6 hours before or 2 hours after ciprofloxacin does not alter the bioavailability of ciprofloxacin. Likewise, a randomized cross-over study with 12 healthy subjects by Frost RW, Lasseter KC et al, 1992 shows that 1800 mg of aluminum (note: very high dose of aluminum) taken 5 min before ciprofloxacin gives a relative bioavailability of ciprofloxacin of 15% . Hoffken G, Borner K et al, 1985 show that the bioavailability of ciprofloxacin is reduced by 94% when ciprofloxacin is given after 10 doses of Maalox over 24 hours. In this study, Maalox is given in 6 times the recommended dose. Calcium Several

studies (Sahai J, Healy DP et al, 1993; Neuhofel AL, Wilton JH et al, 2002; Hoogkamer JF and Kleinbloesem CH1995 and Kato R, Ueno K et al, 2002) show that concomitant treatment with calcium and ciprofloxacin decreases bioavailability of ciprofloxacin by 30-50%. Frost RW, Lasseter KC et al, 1992 show that the relative bioavailability of ciprofloxacin is reduced to 60% by concomitant treatment with calcium. In this study, calcium is used for 3 times the recommended daily dose.

Ofloxacin

Aluminum and magnesium

2 studies show that the bioavailability of ofloxacin is not significantly altered by concomitant treatment with aluminum, Sanchez NA, Martinez CM et al, 1994a (crossover study with 10 healthy subjects) and Martinez CM, Sanchez NA et al, 1991 (cross-over study with 9 healthy subjects). By contrast, there are other studies showing that the bioavailability of ofloxacin is significantly altered by concomitant treatment with aluminum: Akerele JO and Okhamafe AO1991 conduct a cross-over study with 5 healthy subjects taking 200 mg ofloxacin concomitantly with 500 mg of aluminum. The bioavailability of ofloxacin by concomitant intake of aluminum when measured in saliva is reduced by 20%. Shiba K, Sakai O et al, 1992 (cross-over study with 6 healthy subjects) and Shiba K, Sakamoto M et al, 1995 (cross-over study with 5 healthy subjects) also show that the bioavailability of ofloxacin is reduced respectively. 44% and 48% when treated with aluminum simultaneously. A further study conducted on patients with chronic bronchitis shows that Maalox does not significantly alter Cmax of ofloxacin, Maesen FP, Davies BI et al, 1987. Akerele JO and Okhamafe AO, 1991 show that the bioavailability of ofloxacin does not change significantly in 5 healthy subjects. , which takes 200 mg ofloxacin at the same time as 500 mg of magnesium. In contrast, Shiba K, Sakai O et al, 1992, in a cross-over study with 6 healthy subjects, showed a significant reduction in bioavailability of ofloxacin of 22% when co-administered with magnesium.

Calcium

2 studies show that the bioavailability of ofloxacin is not altered by concomitant treatment with calcium Akerele JO and Okhamafe AO1991 (cross-over study with 5 healthy subjects); Shiba K, Sakai O et al, 1992 (cross-over study with 6 healthy subjects). Flor S, Guay DR et al, 1990 (cross-over study with 15 healthy subjects) shows that the bioavailability of ofloxacin is not affected when treatment with calcium and Maalox are shifted by 2 hours, respectively.

Levofloxacin When co-administered with a 1500 mg calcium carbonate solution and 750 mg levofloxacin daily for 5 days in 5 patients with cystic fibrosis Pai MP, Allen SE et al, 2006 observed a decrease in Cmax of approx. 20%. In the same trial in 5 healthy patients, no significant change in Cmax of levofloxacin was seen.

Moxifloxacin

Aluminum and magnesium

In a non-blind, randomized crossover study conducted with 12 healthy subjects, Stass H, Bottcher MF et al, 2001, it is investigated whether aluminum / magnesium affects the absorption of moxifloxacin. Subjects were given a single dose of 400 mg moxifloxacin alone or concomitantly with 10 ml of Maalox. When moxifloxacin is given concomitantly with Maalox, the AUC and Cmax of moxifloxacin are reduced by approx. 60%. If Maalox is taken either 4 hours

before or 2 hours after moxifloxacin, the AUC and Cmax are only slightly reduced.

Calcium

In a non-blind, randomized cross-over study of 12 healthy subjects, Stass H, Wandel C et al, 2001, it is investigated whether calcium affects the absorption of moxifloxacin. Subjects were given a single dose of 400 mg of moxifloxacin alone or simultaneously with 500 mg of calcium. The result is that no difference in AUC for moxifloxacin is seen when moxifloxacin is taken alone or with calcium.

Mechanism: Aluminum, magnesium and calcium form chemical compounds (chelates) with fluoroquinolones, thereby reducing the absorption of the fluoroquinolones, Lomaestro BM and Bailie GR, 1995.fluoroquinolones

No prospective studies / case studies on interactions between antacids and the otherhave been located in the literature.

Class effect Aluminum, magnesium and calcium form compounds (chelates) with fluoroquinolones, thereby reducing the absorption of the fluoroquinolones. Therefore,should be

fluoroquinolonestaken at least 2 hours before aluminum, magnesium or calcium.

No studies have been conducted describing the effect of the other antacidases on the fluoroquinolones.

6.2 Level 3

Substance A Substance B
documentationdegree
Clinical
recommendation concerning
recommen-
recommen-
Conclusion Special
Problems importance
oxidation
oxidation -
dationstekst
precautions
while using Citizen
Attention
aluminum ciprofloxa
cin
well documented
pronounced combination
You can take
Ciprofloxacin should
bioavailable
You should take
preparations deleted
can be used
this
is taken
similarity of
ciprofloxacin
should be deferred
combination,

a minimum of 2
ciprofloxacin
at least 2 hours
apart, because down ingestion
but be
hours prior to
reduced
until aluminum.
ciprofloxacin time.
pay attention to
aluminum.
significant by
effect special can
at the same time
weakened, precautions.
treatment with
if one on aluminum.
At the same time,
if **aluminum is** ingested either 6 hours or before or 2 hours after ciproflaxacin, no significant change in bioavailability of ciprofloxatin is seen. Mechanism: Aluminum forms chemical compounds (chelates) with ciprofloxacin, reducing the absorption of ciproflaxicin.

Fabric A Fabric B Documentation
s degree
NB
calcium ofloxacin limited
evidence
Clinical
recommen-
Rekommanda-
recommen-
Conclusion particular
problems importance
oxidation
tion Borger
dationstekst
action

by concomitant use possible combination

You might
Ofloxacin
Calcium forms
You should take
compositions should be used
to take
should be consumed
chemical
ofloxacin is
taken offset, with offset
this
minimum 2
compounds
at least 2 hours
because **ofloxacin** intake
combination,
hours before calcium.

(chelates) with
pre- **calcium**.
effect may be time.
but you must
ofloxacin,
weakened if you be
which
at the same attention at
decreases
time get special
absorption of
calcium. ratio
ofloxacin. rules.
Whether this interaction is

clinically relevant remains to be clarified. 2 studies failed to demonstrate clinically relevant interaction.

6.3 References

• *Akerele JO; Okhamafe AO; J Antimicrob Chemother 1991; 28: 87-94; Influence of oral co-administered metallic drugs on ofloxacin pharmacokinetics*

• *Campbell NR; Kara M; Hasinoff BB; Haddara WM; McKay DW; Br J Clin Pharmacol 1992; 33: 115-116; Norfloxacin interaction with antacids and minerals*

• *Flor S; Guay DR; Opsahl JA; Tack K; Matzke GR; Antimicrob Agents Chemother 1990; 34: 2436-2438; Effects of magnesium-aluminum hydroxide and calcium carbonate antacids on bioavailability of ofloxacin*

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Effects of aluminum hydroxide and calcium carbonate antacids on the bioavailability of ciprofloxacin

• *Hoffken G; Borner K; Glatzel PD; Koeppe P; Lode H; Eur J Clin Microbiol 1985; 4: 345; Reduced enteral absorption of ciprofloxacin in the presence of antacids*

• *Hoogkamer JF; Small Blossom CH; Drugs 1995; 49 Suppl 2: 346-348; The effect of milk consumption on the pharmacokinetics of fleroxacin and ciprofloxacin in healthy volunteers*

• *Maesen FP;Davies BI;Geraedts WH;Sumajow CA; J Antimicrob Chemother 1987;19: 848-850; Ofloxacin and antacids [letter]*

• *Martinez CM;Sanchez NA;Colino Gandarillas CI;Dominguez-Gil A; Antimicrob Agents Chemother 1991;35: 2102-2105; Effects of two cations on gastrointestinal absorption of ofloxacin*

• *Neuhofel AL;Wilton JH;Victory JM;Hejmanowsk LG;Amsden GW; J Clin Pharmacol 2002;42: 461-466; Lack of bioequivalence of ciprofloxacin when administered with calcium-fortified orange juice: a new twist on an old interaction*

• *Nix DE;Watson WA;Lener ME;Frost RW;Krol G;Goldstein H;Lettieri J;Schentag JJ; Clin Pharmacol Ther 1989;46: 700-705; Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin*

• *Nix DE;Wilton JH;Ronald B;Distlerath L;Williams VC;Norman A; Antimicrob Agents Chemother 1990;34: 432-435; Inhibition of norfloxacin absorption by antac- ids*

• *Sahai J;Healy DP;Stotka J;Polk RE; Br J Clin Pharmacol 1993;35: 302-304; The influence of chronic administration of calcium carbonate on the bioavailability of oral ciprofloxacin*

• *Sanchez NA;Martinez CM;Dominguez-Gil HA;a Antimicrob Agents Chemother 1994;38: 2510-2512; Oral absorption of ofloxacin administered together with alu- minum*

• *Sanchez NA;Martinez CM;Dominguez-Gil HA;b J Antimicrob Chemother 1994;34: 119-125; Comparative study of the influence of Ca2+ on absorption parameters of ciprofloxacin and ofloxacin*

• *Shiba K;Sakai O;Shimada J;Okazaki O;Aoki H;Hakusui H; Antimicrob Agents Chemother 1992;36: 2270-2274; Effects of antacids, ferrous sulfate, and ranitidine on absorption of DR-3355 in humans*

• *Shiba K;Sakamoto M;Nakazawa Y;Sakai O; Drugs 1995;49 Suppl 2: 360-361; Effects of antacid on absorption and excretion of new quinolones*

• *Sadowski DC; Drug Saf 1994;11: 395-407; Drug interactions with antacids. Mechanisms*

6.4 Eksempel på Abstract/Summary

Following recent concern over probable interactions between the 4- quinolones and metal ions, the effect of co-administered drugs--sodium bicarbonate, potassium citrate, ferrous sulphate, magnesium trisilicate, calcium carbonate and aluminium hydroxide--on the saliva and urine pharmacokinetics of ofloxacin in healthy human volunteers has been investigated. The Cmax and AUC0-9 in saliva were generally in the range 1.05-1.40 mg/L and 4.89-6.16 mg.h/L, respectively, and were unaffected (P less than 0.05) by the metallic drugs, except aluminium hydroxide which lowered these values. Again, only aluminium hydroxide modified the Ka of ofloxacin, resulting in a slower absorption rate. However, none of the metallic drugs altered the T1/2 beta of the

4- quinolone in saliva. In-vitro studies using simulated gastric fluid showed that ferrous sulphate, aluminium hydroxide and calcium carbonate reduced ofloxacin availability to 67.4%, 69.3% and 73.8%, respectively. This effect was ascribed to the formation of complexes between ofloxacin and the metal ions concerned. Substantial correlation between in-vitro and in-vivo availability data was demonstrated in all cases except for ofloxacin combinations with ferrous sulphate and calcium carbonate. In general, there was also good correlation between the saliva and urine data.

Bilag 7 XML-DOKUMENT

7.1 DTD

Nedenstående følger DTD'en for
XML-dokumentet:

<?xml version="1.0" encoding="ISO-8859-1"?> <!-- TOP-DEFINITION ALLE UDTRÆKS-ENTITETER --> <!ELEMENT UDTRAEK (NIVEAU2ER, STOFTYPER, STOFFER, STOFGRUPPER, STOFGRUPPERINGER, SUBSTANSER, PRAEPARATGRUPPERINGER, PRAEPARATER, TEKSTER, REFERENCETYPER, REFERENCER, INTERAKTIONER, INTERAKTION_STOFGRUPPER, NIVEAU3ER, NIVEAU3_STOFFER, REFERENCETILKNYTNINGER, REFERENCESTOFFER, KLINISKEBETYDNINGER, DOKUMENTATIONSGRADER, REKOMMANDATIONER, CYP_NAVNE, CYP_EGENSKABER, CYP_KILDER, LINKSTEDER, LINKTYPER, LINKS)> <!ATTLIST UDTRAEK navn CDATA #REQUIRED > <!-- GENERIC ELEMENTS --> <!ELEMENT br (#PCDATA | a | b | sub | sup | i | u | p | P | B)*> <!ELEMENT sup (#PCDATA | a |

br | b | sub | i | u | p | P | B)*> <!ELEMENT sub (#PCDATA | a | br | b | sup | i | u | p | P | B)*> <!ELEMENT b (#PCDATA | a | br | sub | sup | i | u | p | P | B)*> <!ELEMENT B (#PCDATA | a | br | sub | sup | i | u | p | P)*> <!ELEMENT i (#PCDATA | a | br | b | sub | sup | u | p | P | B)*> <!ELEMENT u (#PCDATA | a | br | b | sub | sup | i | p | P | B)*> <!ELEMENT a (#PCDATA | br | b | sub | sup | i | u | p | P | B)*> <!ELEMENT p (#PCDATA | a | br | b | sub | sup | i | u | P | B)*> <!ELEMENT P (#PCDATA | a | br | b | sub | sup | i | u | p | B)*> <!ATTLIST a dlinkdb

CDATA #IMPLIED dlinkid CDATA #IMPLIED id CDATA #IMPLIED > <!-- STOFTYPER --> <!ELEMENT

STOFTYPER (STOFTYPE)*> <!ELEMENT STOFTYPE (ID_Stoftype, Forkortelse, Navn, Tekst)> <!ELEMENT ID_Stoftype (#PCDATA)> <!ELEMENT Forkortelse (#PCDATA)> <!ELEMENT Navn (#PCDATA)> <!ELEMENT Tekst (#PCDATA | a | br | b | sub | sup | i | u | p | P | B)*> <!-- STOFFER --> <!ELEMENT STOFFER (STOF)*> <!ELEMENT STOF (ID_Stof, ID_Stoftype, Navn, Sortering, Tekst_XML, Dosis, Metabolisering, CYP_DATA?)> <!ELEMENT ID_Stof (#PCDATA)> <!ELEMENT Dosis (#PCDATA)> <!ELEMENT Metabolisering (#PCDATA)> <!ELEMENT CYP_DATA (CYP_EMNE)*> <!ELEMENT ID_CYP_Egenskab (#PCDATA)> <!ELEMENT CYP_EMNE (ID_CYP_Navn, ID_CYP_Egenskab, ID_CYP_Kilde)> <!ELEMENT ID_CYP_Navn (#PCDATA)> <!ELEMENT ID_CYP_Kilde (#PCDATA)> <!-- ELEMENT ID_Stoftype (#PCDATA) IS ALLREADY DEFINED -->

<!-- ELEMENT Navn (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT Sortering (#PCDATA)> <!ELEMENT Tekst_XML (#PCDATA)> <!-- STOFGRUPPER --> <!ELEMENT STOFGRUPPER (STOFGRUPPE)*> <!ELEMENT STOFGRUPPE (ID_Stofgruppe, Navn, Sortering, Tekst_XML)*> <!ELEMENT ID_Stofgruppe (#PCDATA)> <!-- ELEMENT ID_Stoftype (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Sortering (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Tekst_XML (#PCDATA) IS ALLREADY DEFINED --> <!-- STOFGRUPPERINGER --> <!ELEMENT STOFGRUPPERINGER (STOFGRUPPERING)*> <!ELEMENT STOFGRUPPERING (ID_Stofgruppering, ID_Stof, ID_Stofgruppe)*> <!ELEMENT ID_Stofgruppering (#PCDATA)> <!-- ELEMENT ID_Stof (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT ID_Stofgruppe (#PCDATA) IS ALLREADY DEFINED --> <!-- TEKSTER --> <!-- SUBSTANSER --> <!ELEMENT SUBSTANSER (SUBSTANS)*> <!ELEMENT SUBSTANS (ID_Substans, ID_Stof, Substansnav n)> <!ELEMENT ID_Substans (#PCDATA)> <!ELEMENT Substansnavn (#PCDATA)> <!-- PRAEPARATGRUPPERINGER --> <!ELEMENT PRAEPARATGRUPPERINGER (PRAEPARATGRUPPERING)*> <!ELEMENT PRAEPARATGRUPPERING (ID_Praeparatgruppering, ID_Praeparat, ID_Substans)> <!ELEMENT ID_Praeparatgruppering (#PCDATA)> <!-- PRAEPARATER --> <!ELEMENT PRAEPARATER (PRAEPARAT)*> <!ELEMENT PRAEPARAT (ID_Praeparat, Praeparatidentifier, Praeparatnavn, Form, Styrke> <!ELEMENT ID_Praeparat (#PCDATA)> <!ELEMENT Praeparatidentifier (#PCDATA)> <!ELEMENT Praeparatnavn (#PCDATA)> <!ELEMENT Form (#PCDATA)> <!ELEMENT Styrke (#PCDATA)> <!-- TEKSTER --> <!ELEMENT TEKSTER (TEKST)*> <!ELEMENT TEKST (ID_Tekst, Tekst_Beskrivelse, Teksttype)> <!ELEMENT ID_Tekst (#PCDATA)> <!ELEMENT Tekst_Beskrivelse (#PCDATA)> <!ELEMENT Teksttype (#PCDATA)> <!-- REFERENCETYPER -->

<!ELEMENT REFERENCETYPER (REFERENCETYPE)*> <!ELEMENT REFERENCETYPE (ID_Referencetype, Forkortelse, Navn, Sorteringsnr)> <!ELEMENT ID_Referencetype (#PCDATA)> <!-- ELEMENT Forkortelse (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Navn (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT Sorteringsnr (#PCDATA)> <!-- REFERENCETILKNYTNINGER --> <!ELEMENT REFERENCESTOFFER (REFERENCESTOF)*> <!ELEMENT REFERENCESTOF (ID_Referencestof, ID_Referencetilknytning, ID_Stof)*> <!ELEMENT ID_Referencestof (#PCDATA)> <!-- REFERENCETILKNYTNINGER --> <!ELEMENT REFERENCETILKNYTNINGER (REFERENCETILKNYTNING)*> <!ELEMENT REFERENCETILKNYTNING (ID_Referencetilknytning, ID_Interaktion, ID_Reference)*> <!ELEMENT ID_Referencetilknytning (#PCDATA)> <!-- REFERENCER -->

<!ELEMENT REFERENCER (REFERENCE)*> <!ELEMENT REFERENCE (ID_Reference, ID_Referencetype, Ref_Manager_Nr, Forfatter_forkortelse, Abstract_Summary)> <!ELEMENT ID_Reference (#PCDATA)> <!ELEMENT Ref_Manager_Nr (#PCDATA)> <!-- ELEMENT ID_Referencetype (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT Forfatter_forkortelse (#PCDATA)> <!ELEMENT Abstract_Summary (#PCDATA)> <!-- NIVEAU2ER --> <!ELEMENT NIVEAU2ER (NIVEAU2)*> <!ELEMENT NIVEA U2 (ID_Niveau2, Versionsdato, ID_Interaktion, Litteraturgennemgang, Klasseeffekt, Klasseeffekt_Borger?)> <!ELEMENT ID_Niveau2 (#PCDATA)> <!ELEMENT Versionsdato (#PCDATA)> <!ELEMENT ID_Interaktion (#PCDATA)> <!ELEMENT Litteraturgennemgang (#PCDATA | a | br | b | sub | sup | i | u | p | P | B)*> <!ELEMENT Klasseeffekt (#PCDATA | a | br | b | sub | sup | i | u | p | P | B)*> <!ELEMENT Klasseeffekt_Borger (#PCDATA | a | br | b | sub | sup | i | u | p | P | B)*> <!-- INTERAKTIONER --> <!ELEMENT INTERAKTIONER (INTERAKTION)*> <!ELEMENT INTERAKTION (ID_Interaktion, Redigeringsdato, Litteraturdato, Nr)> <!-- ELEMENT ID_Interaktion (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT Redigeringsdato (#PCDATA)> <!ELEMENT Litteraturdato (#PCDATA)> <!ELEMENT Nr (#PCDATA)> <!-- INTERAKTION_STOFGRUPPER --> <!ELEMENT INTERAKTION_STOFGRUPPER (INTERAKTION_STOFGRUPPE)*> <!ELEMENT INTERAKTION_STOFGRUPPE (ID_Interaktion_Stofgruppe, ID_Interaktion, ID_Stofgruppe, ID_Stofgruppe1_Sort, ID_Stofgruppe2_Sort, Sortering_Stofgruppe1, Sortering_Stofgruppe2)> <!ELEMENT ID_Interaktion_Stofgruppe (#PCDATA)> <!-- ELEMENT ID_Interaktion (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT ID_Stofgruppe (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT ID_Stofgruppe1_Sort (#PCDATA)> <!ELEMENT ID_Stofgruppe2_Sort (#PCDATA)> <! ELEMENT Sortering_Stofgruppe1 (#PCDATA)> <!ELEMENT Sortering_Stofgruppe2 (#PCDATA)> <!-- NIVEAU3ER--> <!ELEMENT NIVEAU3ER (NIVEAU3)*> <!ELEMENT NIVEAU3 (ID_Niveau2, ID_Niveau3, ID_Dokumentationsgrad, ID_KliniskBetydning, ID_Rekommandation, Tekst, Tekst_Borger?, Rekommandationstekst, ID_Stof1, ID_Stof2)> <!-- ELEMENT ID_Niveau2 (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT ID_Niveau3 (#PCDATA)> <!ELEMENT ID_Dokumentationsgrad (#PCDATA)> <!ELEMENT ID_KliniskBetydning (#PCDATA)> <!ELEMENT ID_Rekommandationstekst (#PCDATA)> <!ELEMENT ID_Rekommandation (#PCDATA)> <!ELEMENT ID_Stof1 (#PCDATA)> <!ELEMENT ID_Stof2 (#PCDATA)> <!ELEMENT Tekst_Borger (#PCDATA | a | br | b | sub | sup | i | u | p | P | B)*> <!-- ELEMENT Tekst (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT Rekommandationstekst (#PCDATA | a | br | b | sub | sup | i | u | p | P | B)*> <!-- NIVEAU3_STOFFER--> <!ELEMENT NIVEAU3_STOFFER (NIVEAU3_STOF)*>

<!ELEMENT NIVEAU3_STOF (ID_Niveau3_Stof, ID_Niveau3, ID_Stof, ID_Stof1_Sort, ID_Stof2_Sort, Sortering_stof1, Sortering_stof2)> <!ELEMENT ID_Niveau3_Stof (#PCDATA)> <!-- ELEMENT ID_Niveau3 (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT ID_Stof (#PCDATA) IS ALLREADY DEFINED --> <!ELEMENT ID_Stof1_Sort (#PCDATA)> <!ELEMENT ID_Stof2_Sort (#PCDATA)> <!ELEMENT Sortering_stof1 (#PCDATA)> <!ELEMENT Sortering_stof2 (#PCDATA)> <!-- KLINISKEBETYDNINGER--> <!ELEMENT KLINISKEBETYDNINGER (KLINISKBETYDNING)*> <!ELEMENT KLINISKBETYDNING (ID_KliniskBetydning, Forkortelse, Navn, Tekst)> <!-- ELEMENT ID_KliniskBetydning (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Forkortelse (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Navn (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Tekst (#PCDATA) IS ALLREADY DEFINED --> <!-- DOKUMENTATIONSGRADER --> <!ELEMENT DOKUMENTATIONSGRADER (DOKUMENTATIONSGRAD)*> <!ELEMENT DOKUMENTATIONSGRAD (ID_Dokumentationsgrad, Forkortelse, Navn, Tekst)> <!-- ELEMENT ID_Dokumentationsgrad (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Forkortelse (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Navn (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Tekst (#PCDATA) IS ALLREADY DEFINED --> <!-- REKOMMANDATIONSTEKSTER --> <!ELEMENT REKOMMANDATIONER (REKOMMANDATION)*> <!ELEMENT REKOMMANDATION (ID_Rekommandation, Tekst, Tekst_Borger?, Sorteringsnr)> <!-- ELEMENT ID_Rekommandationstekst (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Tekst (#PCDATA) IS ALLREADY DEFINED --> <!-- ELEMENT Sorteringsnr (#PCDATA) IS ALLREADY DEFINED --> <!-- CYP_NAVNE --> <!ELEMENT CYP_NAVNE (CYP_NAVN)*> <!ELEMENT CYP_NAVN (ID_CYP_Navn, CYP_Navn)> <!ELEMENT CYP_Navn (#PCDATA)> <!-- CYP_EGENSKABER --> <!ELEMENT CYP_EGENSKABER (CYP_EGENSKAB)*> <!ELEMENT CYP_EGENSKAB (ID_CYP_Eg enskab, CYP_Egenskab_Tekst)> <!ELEMENT CYP_Egenskab_Tekst (#PCDATA)> <!-- CYP_KILDER --> <!ELEMENT CYP_KILDER (CYP_KILDE)*> <!ELEMENT CYP_KILDE (ID_CYP_Kilde, CYP_Kilde_Tekst)> <!ELEMENT CYP_Kilde_Tekst (#PCDATA)> <!-- LINKSTEDER --> <!ELEMENT LINKSTEDER (LINKSTED)*> <!ELEMENT LINKSTED (ID_LinkSted, Tekst)> <!ELEMENT ID_LinkSted (#PCDATA)> <!-- LINKTYPER --> <!ELEMENT LINKTYPER (LINKTYPE)*> <!ELEMENT LINKTYPE (ID_LinkType, Tekst)> <!ELEMENT ID_LinkType (#PCDATA)> <!-- LINKS --> <!ELEMENT LINKS (LINK)*> <!ELEMENT LINK (ID_Link, ID_LinkType, ID_LinkSted, ID_LinkEjer, ID_LinkReferent, ID_Interaktion, LinkTekst)> <!ELEMENT ID_Link (#PCDATA)> <!ELEMENT ID_LinkEjer (#PCDATA)> <!ELEMENT ID_LinkReferent (#PCDATA)> <!ELEMENT LinkTekst (#PCDATA)>

7.2 XSD

Nedenstående følger XSD'en for XML V3 professionel:

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    </xs:complexType> </xs:element> <xs:element
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```

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type="xs:string" /> <xs:element name="Sorteringsnr"
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name="LINKSTED">
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<xs:element name="Tekst" type="xs:string" />
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name="LINKTYPE">
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</xs:sequence> </xs:complexType> </xs:element>
<xs:element name="LINKS">
<xs:complexType>
<xs:sequence>
<xs:element maxOccurs="unbo unded"
name="LINK">
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<xs:sequence>
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name="ID_LinkType" type="xs:string" /> <xs:element
name="ID_LinkSted" type="xs:string" /> <xs:element
name="ID_LinkEjer" type="xs:string" /> <xs:element
name="ID_LinkReferent" type="xs:string" /> <xs:element
name="ID_Interaktion" type="xs:string" /> <xs:element

```
    name="LinkTekst" type="xs:string" /> </xs:sequence>
    </xs:complexType> </xs:element> </xs:sequence>
    </xs:complexType> </xs:element>
</xs:sequence> <xs:attribute name="navn" type="xs:string"
use="required" /> <xs:attribute name="version" type="xs:string"
use="required" /> </xs:complexType> </xs:element>
</xs:schema>
```

7.3 Databasediagram

Databasediagrammet viser sammenhængene mellem de forskellige tabeller i XML-dokumentet: