Report on the contrast agent Omniscan®

The Danish Medicine Agency
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1. Background for the Report

Omniscan® is a contrast agent used for MR scannings. Omniscan® was approved in Denmark in 1994.

In the spring of 2006 The Danish Medicines Agency received a number of reports of NSF (nefrogen systemic fibrosis) adverse drug reactions in connection with the use of Omniscan® for kidney patients at Herlev Hospital. The Danish Medicines Agency had not had any previous reports of adverse drug reactions linking Omniscan® to NSF.

Immediately afterwards, The Danish Medicines Agency – as the first authority in Europe – issued a warning to the public about the suspicion raised by the reports as to the risk of serious adverse drug reactions. At the same time, The Danish Medicines Agency brought the issue before the EU Council for Adverse Drug Reactions.

The Council decided on 22 January 2007 to advise against the use of Omniscan® for people with reduced renal function. The product information for Omniscan® was changed accordingly on 5 February 2007.

In February 2008 physicians Casper Rydahl, Henrik Thomsen and Peter Marckmann published an article about NSF and the use of Omniscan® in patients with severe renal problems. This article and the consequences for those patients afflicted with NSF after having had Omniscan® injected in connection with an MR scanning, were mentioned in depth in the publication “Dagens Medicin” on 22 February 2008.

It was against this background that the Secretary of State for Health and Prevention ordered a report about Omniscan®.

The Report contains the following:

- **Section 2** describing Omniscan®.
- **Section 3** dealing with the requirements for authorisation of drugs and also with the actual authorisation of Omniscan® in 1994, including the knowledge about release of gadolinium in the body available at the time of authorisation.
- **Section 4** describes conditions under which an authorisation can be revised and the revisions to the authorisation of Omniscan® (summary of product characteristics) that have taken place since 1994.
- **Section 5** contains a description of the adverse drug reaction system, an exposition of toxic implications in relation to gadolinium, a short resume of known adverse drug reactions of Omniscan®, a description of the disease NSF and an overview of articles and theories about NSF.

The section further contains a summary of the adverse drug reaction reports regarding Omniscan® received by The Danish Medicines Agency or registered in the European Adverse Drug Reaction Database, and of the Periodic Safety Update Reports submitted to The Danish Medicines Agency.

- **Section 6** contains an in-depth review of the sequence of events from when The Danish Medicines Agency received the first reports of adverse drug reactions relating to NSF and Omniscan® in 2006 till now.
- **Section 7** deals with the possible risks concerning the use of Omniscan® in people with normal renal function.
• Section 8 deals with the general terms for revising, suspending or recalling the authorisation of a drug and it assesses whether these conditions were met in the case of Omniscan®.
• Section 9 contains information about the use of Omniscan® in Denmark.

2. Omniscan®

2.1. Applications
Omniscan® is a contrast agent used for MR scannings (magnetic resonance imaging (MRI)). The drug is injected into the patient and increases the contrast in the picture the doctor sees during the scanning.
The approved area of application (the therapeutic indications) for Omniscan® is in accordance with the prevailing summary of product characteristics:

"Contrast agent for magnetic resonance imaging (MRI) at cranial and spinal tomography and for general MRI of the whole body after intravenous administration. Product indications for cardiologic MRI examinations are for coronary arterial diseases immunoardial perfusions MRI (stress/rest and late examinations), detection and localisation of coronary arterial illnesses and differentiation between areas with ischemia and infarction in persons with known or suspected coronary arterial disease."

MR contrast examinations are generally used when serious disease is suspected. Patient with chronic renal disease have a high incidence of cardiovascular diseases and are therefore often in need of vascular examinations including evaluation of the state of the blood vessels to assess the possibility of surgical vascular treatment of circulatory problems, evaluation of suitability for kidney transplants and assessment of the setting up of a vascular dialysis access. Previously, conventional X-ray contrast examinations were used. However, X-ray contrast agents are renally toxic and the use thereof in patients with reduced renal function entails the risk of permanent renal failure.
When MR contrast examinations were introduced they were a clinical gain to kidney patients.

2.2. Active Components
Omniscan® contains the heavy metal gadolinium in a concentration of 0.5 mmol/ml in the form of gadodiamid. Gadodiamid is eliminated by the kidneys. In patients with normal renal function, about 85 pct. of the administered dose will have been eliminated four hours after the injection and 95-98 pct after 24 hours. In patients with reduced renal function it takes longer to eliminate. Omniscan® is one of several contrast agents containing gadolinium for MR scannings. They all contain gadolinium as trivalent ion (Gd³⁺) and an organic carrier molecule that binds the gadolinium ion in a complex. Gd³⁺ gives the contrast effect while the carrier molecule rules how the complex and thereby the gadolinium is distributed in the body and eliminated from the organism.
Gadolinium has no known biological function and is normally not found in the organism.
3. Authorisation of Omniscan®
Omniscan® was authorised by The Danish Medicines Agency in 1994.

3.1. Authorisation of Medicines in General
Drugs have to be approved by The Danish Medicines Agency or the European Commission, before they can be sold on the Danish market. This is stipulated in the Drugs Act § 7:

“A medicinal product may only be marketed or dispensed in Denmark when a marketing authorisation has been granted either by the Danish Medicines Agency pursuant to this Act or by the European Commission pursuant to the provisions of Community law laying down Community procedures for authorisation and pharmacovigilance of medicinal products for human and veterinary use etc. (Community marketing authorisation)”

The requirement for authorisation was also in force in 1994, when the provision was found in the Medicines Act § 13, item 1.
A precondition for the authorisation of a drug is that there is a favourable balance between the effect of the drug and the risks entailed in its use. This balance is a very critical element in the authorisation of new drugs as well as in the monitoring of drugs already on the market. Those applying for authorisation of a drug must document the effect of the drug, its safety and quality and any possible environmental effect to The Danish Medicines Agency.
Based on this documentation The Danish Medicines Agency will consider the benefits contra the risks, see the Medicines Act § 8, item 2:

“When assessing the balance between benefits and risks of a drug the positive therapeutic effect will be assessed against the risks of using the drug, its quality, safety and effect and the risk of any unwanted environmental effects...”

As part of the authorisation of a drug The Danish Medicines Agency will also approve the summary of product characteristics, which contains a whole range of information about the drug, including the approved effect, adverse drug reactions, administration, warnings, contraindications (circumstances that speak against the use of the drug).
More detailed information about the requirements for the documentation that companies must provide as part of the application for authorisation of a drug can be found in the regulation on marketing permissions for drugs, etc.

3.2. Application and authorisation – Omniscan®
The application for authorisation of Omniscan® was submitted to The Danish Medicine Agency on 4 February 1993 after the prevailing multistate procedure, which preceded the present mutual recognition procedure.
When the application was submitted (in this country and in ten other EU countries) Omniscan® was already approved in Great Britain. The Danish Medicine Agency based its assessment on the British authorisation, but an independent Danish assessment was undertaken based on the complete application submitted.
The application indicated that rats showed signs of skin changes in two studies of 21 and 28 days duration respectively. The applicant put these findings down to zinc deficiency resulting from an increased elimination of zinc. So, as it is well known that rats react to zinc deficiency, this explanation was accepted by The Danish Medicine Agency. For further information see section 5.2 About toxicology.

The Danish Medicine Agency assessed, in accordance with the applicant, that Omniscan® should not be used in kidney patients, as clinical trials with that type of patients still had to be undertaken. Therefore, the applicant proposed that Omniscan® was contraindicated for patients with reduced renal function.

Omniscan® was authorised by The Danish Medicine Agency on 18 January 1994. The authorisation (the marketing authorisation) see attached appendix 1 and the summary of product characteristics used as appendix 2.

The summary of product characteristics section 4.3 indicated that Omniscan® was contraindicated in cases of: “Hypersensitivity to Omniscan®. Reduced renal function. Must not be administered to patients below 18 years”.

Furthermore the summary of product characteristics specifies that the approved indication was “magnetic resonance imaging (MRI) for cranial and spinal tomography” and that the dosage was “0.1 mmol pr. kg b.w. (equalling 0.2 ml pr. kg b.w.) up to 100 kg. In case of b.w. above 100 kg 20 ml will normally suffice.”.

Following its authorisation Omniscan® has had status as a nationally approved drug.

3.2.1. The Marketing Authorisation Holder
Nycomed A/S was the marketing authorisation holder for Omniscan® from its authorisation until 22 July 1994. Since then the marketing authorisation has changed hands several times:

**Omniscan® Marketing Authorisation Holders**
26 January to 22 July 1994 Nycomed A/S
22 July 1994 to 12 December 2001 Nycomed Imaging AS
12 December 2001 to 23 May 2006 Amersham Health A/S
From 23 May 2006 GE Healthcare A/S

3.3. Release of Gadolinium in the body
In the journal Dagens Medicin of 14 March 2008 there was a mention that “trials with mice and rats (that) indicated that after the use of Omniscan® large amounts of the extremely poisonous free gadolinium could be traced in the bones, the liver and the whole body in amounts that were considerably larger than after the use of other MR contrast agents”.

One of these trials is described in an article published in Magnetic Resonance Imaging in 1992, i.e. prior to the authorisation of Omniscan®. In this trial mice were injected with seven different radioactive (Gd-153) gadolinium complexes intravenously including substances corresponding to the contrast agents Gadovist®, Prohance®, Dotarem®, Magnevist® and Omniscan®. The mice were killed respectively at 5 minutes, one hour, one or seven days or two weeks after the injection and the levels of radioactivity were established in the different
organs and in the rest of the mice (the carcases). All five contrast agents were quickly eliminated with the urine, however seven days and two weeks after the injection the conclusion was that there were about ten times more radioactivity left in the mice that were given Gadovist® and Omniscan® as in those mice that had been given Prohance®, Dotarem® or Magnevist® (approx. 1 pct. against approx. 0.1 pct. of the injected amount).

This article was not included in the documentation material attached to the application for authorisation of Omniscan®. The reason for this could be that the application submitted in Denmark was identical to the application submitted in Great Britain in 1991, i.e. prior to publication of the article.

However, included in the documentation material was another trial, which compared Omniscan® with Magnevist®. This trial showed that when Omniscan® was used greater amounts of gadolinium were left in the liver and the kidneys in mice and rats than when Magnevist® was used.

It is not evident from the authorisation case of 1994 specifically how The Danish Medicine Agency regarded this knowledge. However, one must conclude that it was not considered of importance to the balance between benefits and risks in the use of Omniscan®. This must of course be seen in the context that Omniscan® from the beginning was contraindicated for the use in patients with reduced renal function, as mentioned above.

Likewise, one must conclude that the British authorities did not regard this circumstance as significant either, when Great Britain authorised Omniscan® in 1992 as the first country in Europe.

### 3.3.1. Mosby Year Book 1992

The journal Dagens Medicin of 22 February 2008 mentions that "American scientists in 1992 (had) in the Mosby Year Book 1992... documented that the risk of poisoning with the dangerous heavy metal gadolinium was far bigger with Omniscan® than with most other types of MR contrast agents". Furthermore, it transpires from the article that "linear contrast agents increase the risk of the poisonous heavy metal gadolinium being released in the body. Up to 10 times as much poisonous gadolinium is released from linear substances like Omniscan®".

This assessment in Mosby Year Book 1992 has to be based on the trial that was published that same year and is described above in item 3.3. In this trial there were, after two weeks, about ten times more of the contrast agent left in the mice that had been given Gadovist® and Omniscan®, than in those mice that had been given one of the other contrast agents. However, the measuring technique (radioactive gadolinium) raises uncertainty about whether it was the free – thereby poisonous – gadolinium that was left in the mice, or whether it was the total – and not very poisonous – gadolinium-containing complex that was left.

Therefore, it is incorrect to conclude that up to ten times as much of the poisonous gadolinium is released from linear contrast agents such as Omniscan® than from other (cyclical) contrast agents.

Furthermore, that same trial showed that the linear contrast agent Magnevist® did not leave much higher concentrations than the cyclical ones. And there are trials with mice that show that Omniscan® is less poisonous than other contrast agents containing gadolinium.
The conclusion in the Mosby Year Book was that in clinical practice the use of linear as well as
cyclical gadolinium complexes is efficient, safe and well-tolerated.

4. Revision of the Authorisation of Omniscan®
Since the authorisation of Omniscan® in 1994 the summary of product characteristics has been
revised a number of times. The most important revisions are evident in item 4.2.

4.1. About revision of an authorisation of a drug in general
Authorisation of a drug, including the summary of product characteristics attached to the
authorisation, can be revised either by the company, which has the marketing authorisation, or
under special circumstances, at the instigation of The Danish Medicines Agency.
Should a company wish to revise the summary of product characteristics or other documents; it
has to apply for permission from The Danish Medicines Agency. This is done with the use of a so
called Application for Revision, see the Medicines Act § 26, item 1:
“The holder of the marketing authorisation issued by The Danish Medicines Agency must apply for
permission for every revision in the summary of product characteristics and the documents upon
which the marketing authorisation has been granted (Application for revision)”.
The Danish Medicines Agency assesses the application and the documentation the company
submits as a basis for the revision applied for.
The Danish Medicines Agency can make revisions to an authorisation on the conditions
stipulated in the Medicines Act §§ 14-16, including if:
• The balance between benefits and risks of the drug is unfavourable (§ 14,
  item 1, No. 1).
• Important information supplied in support of the application for authorisation of the drug is
  incorrect (§ 14, item 1, No. 4).
• The company makes changes to the summary of product characteristics or to the documents
  upon which the marketing authorisation is based without the consent of The Danish Medicines
  Agency (§ 14, item 2, No. 3).
• The company has not submitted new information about the balance between benefits and risks
  of the drug to The Danish Medicines Agency in accordance with the Medicines Act § 25, item 1 (§
  15, No. 2).

4.2. Revision of the summary of product characteristics

4.2.1. Revision of contraindications, 1994
On 6 May 1994 the marketing authorisation holder for Omniscan® applied to revise – or clarify –
the contraindication from “Reduced renal function” to: “Severe renal insufficiency (GFR < 30
ml/min.)” The background for this was that trials had shown that the product could be used in
patients with moderately reduced renal function.
The contraindication was changed in the summary of product characteristics dated 22 July 1994.
The summary of product characteristics is attached as appendix 3.
4.2.2. Revision of dosage and application, 1995
An examination of 600 patients had shown that an increase of the dose often resulted in improved diagnostic information. There were no signs that the risk of adverse drug reactions was increased through the higher dosage. Against this background the dosage was changed in a way that upon "suspicion of brain metastasis a dose of 0.3 mmol/kg b.w. can..... be administered (corresponding to 0.6 ml/kg bodyweight) up to 100 kg."
At the same time the area of application was revised from consisting of adults only also to include children down to the age of six months.
Summary of product characteristics dated 9 August 1995 is attached as appendix 4.

4.2.3. Revision of indication, 1996
In July 1996 the indication was widened to include general MR scanning of the whole body. The widening was based on a trial, scanning different organs in about 750 patients. Only very few adverse drug reactions were found during the trial. The widened area of indication can be seen in the summary of product characteristics of 31 July 1996 which is attached as appendix 5.

4.2.4. Revision of contraindications and new warning, 1998
In 1997, the marketing authorisation holder of Omniscan® applied to have the contraindication for patients with reduced renal function deleted. With this application the marketing authorisation holder submitted an expert report prepared by Professor Henrik Thomsen on 29 April 1997. From this it appeared that the basis for the application was the results of five clinical trials involving a total of 49 patients with severely reduced renal function. Only few adverse drug reactions occurred and the incidence of adverse drug reactions in patients with severely reduced renal function was no higher than in healthy people. There were no cases of skin changes. For the trials the low dose of 0.1 mmol/kg was used. In the expert report Henrik Thomsen concludes "It is documented that gadodiamide injection at a dose of 0.1 mmol/kg b.w. is safe and well tolerated in patients with severely reduced renal function (GFR <30 ml/min.) or with end-stage renal failure treated with dialysis (haemodialysis or peritoneal dialysis). Gadodiamide behaves in the body exactly as the other well known contrast media for radiological procedures and MRI procedures. Severely reduced renal function or replacement therapy does not contraindicate the use of gadodiamide. No special procedures e.g. daily haemodialysis for three days are necessary". The expert report is attached as appendix 6.
At the same time the marketing authorisation holder wanted to add two warnings to the summary of product characteristics referring to anaphylactic shock and problems with the use of Omniscan® in patients with severely reduced renal function.

After about 5 million people having been treated with Omniscan®, adverse drug reactions were encountered in 1-2 pct. of patients treated with 0,1-0,2 mmol/kg b.w.– irrespective of the speed of injection and occurrence of kidney disease. In a few patients with severely reduced renal function there was a certain additional reduction in GFR (renal filtration
GFR (renal filtration speed, i.e. the amount of liquid pr. time unit filtered through the kidneys). Only very few serious adverse drug reactions were observed and there were no reports of skin changes. In addition a few but life-threatening cases of anaphylactic reactions to the treatment with Omniscan® were reported.

The marketing authorisation holder also referred to a periodical safety update (PSUR) from March 1997 in which these cases of anaphylactic shock were described. The Danish Medicines Agency accepted all the revisions that had been applied for. It does not appear that any specific assessment about the removal of the contraindication was made. The contraindication for renal patients was, against this background, deleted from the summary of product characteristics, and warnings were added, on the one hand about life-threatening anaphylactic shock and on the other about additionally reduced renal function in patients who were already suffering from reduced renal function. This latter warning was formulated as follows:

"In a few patients with sever renal insufficiency (GFR < 10 ml/min.) a further minimal reduction of GFR has been observed without any signs of nephrotoxicity in connection with the administration of Omniscan®. The clinical significance of these observations is not yet known, Omniscan® should therefore be used with caution in these patients”.

In connection with these revisions of the summary of product characteristics there does not seem to have been any consideration with regard to shortening the interval of dosage in patients with reduced renal function. The summary of product characteristics dated 30 March 1998 is attached as appendix 7. Contraindications for renal patients were not only deleted in Denmark but also in a number of other countries including Belgium, Finland, France, Eire, Island, The Netherlands, Norway, Great Britain, Switzerland, Sweden, Germany and Austria.

4.2.5. Revision of age limit 1999
In the Summary of Product Characteristics of 17 August 1999 the age limit for treatment of children with Omniscan® was partially removed. The Summary of Product Characteristics is attached as appendix 8.

4.2.6. Administration, etc. in case of coronary disease 2005
In 2005, the summary of product characteristics was extended with a special section on administration in relation to MR scanning in cases of coronary diseases. The summary of product characteristics of 1 August 2005 is attached as appendix 9

4.2.7. New contraindications, new warning and mention of NSF, 2007
The summary of product characteristics was revised several times during 2007. The background for these revisions is dealt with in greater detail in section 6 about the sequence of events 2006 – 2008.

In the summary of product characteristics dated 5 February 2007 Omniscan® was again contraindicated for patients with severely reduced renal function. Furthermore, a warning was added about NSF being linked between the use of Omniscan® (and a few other contrast agents containing gadolinium) in patients with severe renal failure and NSF was added to the section
about adverse drug reactions. The summary of product characteristics is attached as appendix 10.
The current summary of product characteristics is dated 28 June 2007. As a follow-up to a decision by the EU Council for Adverse Drug Reactions a warning that NSF had been encountered in patients with moderately reduced renal function was added.

“There are reports of cases of NSF in patients with moderate renal failure (GFR <60 ml/min/1,73m2) [treated] with gadodiamid. Therefore, Omniscan must be used with caution in these patients.”

The summary of product characteristics is attached as appendix 11.

5. Adverse drug reactions to Omniscan®
It is a prerequisite for the authorisation of a drug that there is documentation for the safety of the drug including the risk of adverse drug reactions.
Irrespective of how thorough the studies performed prior to authorisation are, there is, unfortunately, always a risk that unknown adverse drug reactions will occur once the drug is introduced and used in far greater scale than during the trials that formed the basis for the authorisation. Therefore, the company that is the marketing authorisation holder as well as the doctors using the drug for their patients must inform The Danish Medicines Agency of any adverse drug reactions that occur in practice.

5.1. General Periodic Safety Update Reporting (PSUR) of adverse drug reactions
It is important for the pharmaceutical companies as well as for the health authorities that the occurrence of adverse drug reactions from a drug can be monitored after the drug has been introduced in the market. Therefore, there are several parallel systems that contribute to the collection, registration and utilization of information on adverse drug reactions that occur once the drug is in use.

5.1.1. Medical Practitioners
Medical practitioners are obliged to report all adverse drug reactions they encounter in patients under their treatment, in the case of a new drugs, i.e. drugs that have been in use for less than two years,
If the drug has been authorised more than two years the obligation to report only covers severe and unexpected adverse drug reaction. The obligation to report has been made more stringent several times and was given its current content in 2003.
Further to the adverse drug reactions medical practitioners are obliged to report, they can report all adverse drug reactions that they get to know about.

Rules about medical practitioners’ reporting of adverse drug reactions can be seen in the regulation on reporting of adverse drug reactions in drug, etc. The regulation is attached as appendix 12.
Despite the importance of reporting adverse drug reactions as part of the monitoring of drug safety and irrespective of the extended obligation medical practitioners have to report adverse drug reactions, it is a well known fact that medical practitioners only report a fraction of the adverse drug reactions they come across. There are several possible reasons for this. Among the
reasons given by the practitioners themselves is that they do not have sufficient time, that it is too onerous, and that they are not paid to report. The fact that it does not give any credits to report adverse drug reaction could not be ruled out either. Finally the practitioner might – although without reason – be of the opinion that reporting adverse drug reactions does not change anything.

Reports of adverse drug reactions are mainly a statistical tool to be used when assessing the safety profile of a drug. The Danish Medicines Agency uses the reports as a basis for the ongoing assessment of the products on the market. However, each single report will not, be used as a basis to undertake an assessment of whether the reported adverse drug reactions have a connection to the drugs mentioned in the reports.

An overall assessment of the reported adverse drug reactions of a drug is undertaken in connection with the periodic evaluation of the safety update reports from the holders of the Marketing Authorisation of the drug.

The Danish Medicines Agency will pass on the reported information about adverse drug reactions to the company that holds the marketing authorisation for the drug, to the European Adverse Drug Reaction Database that is administered by EMEA (The European Medicines Agency) and to WHO.

5.1.2. Companies

The company that is the marketing authorisation holder for a drug must in accordance with the Medicines Act § 53, item 1. 1,
1) keep records of suspected adverse drug reactions,
2) put the records at the disposal of The Danish Medicines Agency,
3) report information of adverse drug reactions to The Danish Medicines Agency and
4) prepare and submit periodical safety updates (PSURs) to The Danish Medicines Agency.

Further rules and regulations about the companies’ collection and reporting of information on adverse drug reactions are to be found in the regulation regarding monitoring of drugs and the regulations regarding obligations relating to reporting of adverse drug reactions and PSURs, etc.

This shows that the marketing authorisation holder for a drug must keep detailed records of all adverse drug reactions that the company could reasonably be expected to know about, irrespective of where in the world the adverse drug reactions have occurred. These records must be submitted to The Danish Medicines Agency as PSURs. PSURs must be submitted to The Danish Medicines Agency at fixed intervals:

Every six month during the first two years after a drug has been introduced, once a year after two years and every three years thereafter. Furthermore, marketing authorisation holders must prepare a PSUR outside these dates should The Danish Medicines Agency ask for it.

If the holder of the authorisation gets to know of serious, unexpected adverse drug reactions the holder must immediately or no later than within two weeks, report this to The Danish Medicines Agency, to the authorities in the reference country (the country that handles procedures on behalf of all EU countries) or to EMEA.

As Omniscan® is a nationally authorised drug, adverse drug reactions occurring in this country must be reported to The Danish Medicines Agency.
5.1.3 The Danish Medicines Agency’s handling of adverse drug reaction reports

The Danish Medicines Agency keeps a register of reported adverse drug reactions, see the Medicines Act § 56, item 1. This register is normally called The Danish Medicines Agency’s Adverse Drug Reaction Database.

In accordance with the regulation concerning adverse drug reaction monitoring of drugs The Danish Medicines Agency must within two weeks after receipt of reports of suspected serious adverse drug reactions registered in Denmark, pass these reports on to EMEA, to the authorities in the other EU and EØS countries [a cooperation between the three European countries Ireland, Norway and Liechtenstein and the EU countries] and to the marketing authorisation holder. The Danish Medicines Agency compares the information about adverse drug reactions and reactions to exposure reported with existing information about the use of the drug that may impart on the assessment of benefits and disadvantages of the drug.

It is quite evident from the notices to the Medicines Act (proposed legislation No. L 189 about changes to the Medicines Act and Pharmacies Act of 2002-03) that each individual company holds the primary responsibility for the drugs it markets:

“It is the companies that have the responsibility for the safety of their drugs and all reports of adverse drug reactions are included in the systematic safety assessment of each product. The reports are included in the PSUR that all holders of a Marketing Authorisation must prepare and submit to The Danish Medicines Agency at regular intervals. In the safety report the company must examine and assess all adverse drug reaction reports received (including those from other countries) about the products it markets and compare them to the utilisation and published studies. If serious adverse drug reactions are demonstrated the company must inform the Danish Medicine Agency at once.

... Adverse drug reaction reports constitute a statistical tool to be used in the assessment of the safety profile of a drug. The Danish Medicine Agency uses the reports as a basis for the ongoing assessments of marketed products, but does not on the basis of individual reports undertake assessments of whether one or more of the reported adverse drug reactions have a real connection with the drugs listed in the reporting form. An overall assessment of the reported adverse drug reactions will be undertaken in connection with the handling of the PSUR for the holders of the Marketing Authorisation.”

5.2. Toxicology

The toxicological investigations of Omniscan® (gadodiamid) were conducted about 20 years ago. There are a total of four investigations with repeated administration by intravenous injection:

- One 21-day trial with rats treated three times pr. week with 0, 0.1, 2 or 5 mmol/kg (9 dosis in total).
- One 28-day trial with rats treated daily with 0, 0.01, 0.05 or 0.25 mmol/kg (28 dosis in total).
- One 22-day trial with monkeys treated 3 times pr. week with 0, 0.1 or 5 mmol/kg (9 dosis in total).
- One 28-day trial with monkeys treated daily with 0, 0.05, 0.25 or 1.25 mmol/kg (28 treatments).
In both rat trials there were skin changes in the shape of loss of hair, thickening of the skin and wound and scab formations in some of the animals that received the highest doses. Neither the company behind Omniscan® nor The Danish Medicine Agency attributed any clinical significance to these changes in connection with the application for authorisation of the product. This could be due to several factors:

- Firstly the skin changes only occurred in rats that were treated several times with doses above the stipulated 0.1mmol/kg b.w.
- Secondly, there were no skin changes in monkeys, which biologically are closer to humans than rats.
- Thirdly, the applicant explained in an expert report that the changes were due to the fact that the treatment involved an increased elimination of zinc causing zinc deficiency. It is a well known fact that rats react to zinc deficiency.

Bayer Schering has only recently submitted trial results that show skin changes in rats, comparable to NSF in humans, when they were treated with gadoiamid 2.5 mmol/kg five days a week for four weeks (total of 20 doses). They also found that the treatment produces deposits of gadolinium in the skin – but no deficiency of zinc. The results were presented for the first time at an official hearing organised by the FDA in 2007 but not published till the beginning of 2008. Against this background it is likely that the rat is a relevant model for NSF. It is therefore sensible to calculate the risk factor for NSF based on the original data on rats.

The lowest cumulated toxic dose was 7 mmol/kg. The lowest cumulated non-toxic dose was 1.4 mmol/kg. When taken into account that rats have a higher metabolism pr kg b.w. than people it can be deducted that no skin changes should occur in people treated with a total of up to 0.2 mmol/kg, while skin changes can be expected in people treated with doses corresponding to 1 mmol/kg or more.

Gadodialmid is eliminated unchanged through the kidneys. At normal renal function it is quickly halved in about 70-75 minutes in healthy people. In patients with severely reduced renal function the time span for this is between 13 and 89 hours, in patients in haemodialysis between 2 and 3½ hours, and in patients in ambulatory peritoneal dialysis between 45 and 64 hours.

The strain of gadoiamid on the organism is directly proportional with the time it takes to halve it. Therefore, the strain on patients with severely reduced renal function can be up to 70 times that of patients with normal renal function even if they were given the same dosage.

The possible connection between Omniscan® and the development of NSF has been investigated in a study of 38 patients with severe chronic kidney disease, half of whom had developed NSF while the rest did not have NSF and were used as a control group. The study illustrated that statistically there was a significant connection between the cumulated dose of Omniscan® and the risk of NSF (0.41 mmol/kg in patients with NSF against 0.31 mmol/kg in patients without NSF). Equally there was a statistically significant connection between the cumulated dose and the severity of NSF (0.49 mmol/kg in patients with severe NSF against 0.33 mmol/kg in patients with less severe NSF).

At Herlev Hospital, where, as mentioned below, there seems to be a markedly over representation of cases of NSF, Omniscan® was apparently, over a number of years, the only MR
contrast agent used for patients with renal failure, and the dose normally used was 0.3 mmol/kg (which is the maximum dosage according to the summary of product characteristics for Omniscan®). This is illustrated by two articles published in 2007 and 2008 the authors being, among others, Henrik Thomsen and Peter Marckmann (appendices 13 and 14). The highest cumulated dose is stated as having been 1 mmol/kg corresponding to three scannings per patient. The considerations above are rendered in greater detail and with more calculations and references to published articles in appendix 15.

5.3. Known Adverse drug reactions with Omniscan®
The adverse drug reactions of Omniscan® recognised at present are stated in section 4.8 in the summary of product characteristics, see appendix 11: "Nausea, vomiting, dizziness, indisposition, hypersensitivity reactions, brief changes to the gustatory sense. Anaphylactic reactions occur. Cramps have been observed very rarely. Cases of nefrogen systemic fibrosis (NSF) with Omniscan® have in extremely rare cases been reported. Very rarely (< 1/10.000), unknown (cannot be estimated from available data): Diarrhoea, dyspnoea, trembling, anxiety, tachycardia, pains in the joints, paropsis, chest pains”. The mention of NSF was introduced in the summary of product characteristics on 5 February 2007, see 4.2.7.

5.4. NSF (nefrogen systemic fibrosis)
NSF is characterised by fibrosis of the skin and the internal organs. The pathological picture was first observed in 1997 in the U.S. The first description of the disease was published in the medical journal The Lancet in 2000. The disease was previously called nefrogen fibroserende dermatopati (NFD), because it was believed that the fibrosis only took place in the skin. It has since transpired that the fibrosis also affects internal organs. The name was therefore changed to nefrogen systemic fibrosis. NSF has only been encountered in patients with reduced renal function. Most MR contrast agents that contain gadolinium are almost solely eliminated via the kidneys. The elimination of gadolinium will therefore be considerably slower in people with reduced renal function than in others. The skin of patients with NSF becomes rough, hard and discoloured. In cases of pronounced fibrosis the mobility of the joints can be reduced, which can for instance lead to the patients loosing the ability to walk. Since the first time the diagnosis of NSF was made, a whole range of possible causal factors have been suggested and mentioned in the literature.

5.5. Published articles and theories about NSF and gadolinium
The first scientific article that described a coincidental relation between NSF and prior use of a MR contrast agent containing gadolinium (Omniscan®) was published in January 2006 and
concerned five patients from a dialysis centre in Austria. Among nine kidney patients who had been examined with Omniscan®, five patients developed NSF within two to four weeks. The five patients who developed NSF, had (as opposed to the four others) abnormal pH-values in the blood (metabolic acidosis) at the time of the MR scanning. Furthermore, the five patients with NSF had on average been in dialysis treatment for longer prior to the MR scanning, than was the case for the other four. In August 2006, Peter Marckmann, Henrik Thomsen, et al, published a retrospective investigation of records from the medical renal department of Herlev Hospital (enclosure No. 16). During the period of August 2005 till May 2006, 13 patients were identified, who had been examined with Omniscan® prior to developing NSF. Between 9 and 25 mmol gadodiamid – the type of gadolinium used in Omniscan® – was used per patient (an average of 18.5 mmol). Seven of the patients developed sever degrees of NSF. One patient died, six of the 13 patients had previously been treated with gadodiamid in a quantity of up to 25 mmol without having developed NSF. The investigation did not show any relation between NSF and the pH-value in the blood.

During 2006 scientific circles put forward several hypotheses about why and how the exposure to gadolinium can bring about the development of NSF. These hypotheses were based on the physical-chemical characteristics and molecular structure of contrast agents containing gadolinium as well as clinical and pre-clinical findings. In MR scanning the contrast agent gadolinium is encapsulated in order that the gadolinium does not come into direct contact with tissue. One hypothesis is that gadoliniums, so to speak, are exchanged with other ions, like zinc or copper ions that are naturally found in the body (transmetallation) and that there is a particularly high risk of that happening when Omniscan® is being used because this product is less "stable" – or more accurately: it has a lower komplekskonstant – than the other products. This means that there is a higher concentration of free gadoliniumions in Omniscan®, probably because of a particular molecular structure and specific physical-chemical characteristics. Two other products, which at the beginning of 2007 were also connected to NSF, Magnevist® and Optimark® both, have a molecular structure and physical-chemical characteristics that are fairly similar to those of Omniscan®.

Another hypothesis is that gadolinium – after being released as a consequence of transmetallation- is deposited in the skin. A third hypothesis is that this deposit brings about fibrosis by activating one particular type of cell (fibrocyt), which is formed in and are dispersed from the bone marrow.

5.6. Reports of adverse drug reactions
As per 29 February 2008, the Danish Medicines Agency has received 36 reports of adverse drug reaction diagnosis of NSF. 35 of those concern Omniscan®. Distribution by date and place is as follows:

• 2006: 28 reports of which 27 were from Herlev Hospital and one from Holstebro
Sygehus. One of the reports from Herlev Hospital had been submitted once before, in 2002 already. However, at that time the adverse drug reaction diagnosis was not stated as being NSF but as muscular pain.

- 2007: 7 reports, of which 5 from Herlev Hospital, 1 from Hillerød Sygehus
- 2008: 1 from Herlev Hospital.

In the case of 23 of the 35 reports concerned with Omnisan®, the date of the examination, the onset of the adverse drug reaction and the reporting to the Danish Medicines Agency can be established. The correlations between these dates are shown in table 1.

As of 1 July 2003 Danish medical practitioners were obliged to report all serious, unexpected adverse drug reactions. As can be seen in the table, adverse drug reactions to Omnisan® were reported a long time after they occurred. The cause for this can be one or more of the overall reasons for the lack of reporting of adverse drug reactions as mentioned in section 5.1.1 as well as the fact that the earliest symptoms of NSF are unspecific and difficult to separate from the many other symptoms that a kidney patient suffers from.

Table 1. Adverse drug reaction reporting regarding Omnisan® and NSF

<table>
<thead>
<tr>
<th>Reporting to The Danish Medicines Agency</th>
<th>Date of examination</th>
<th>Adverse drug reaction</th>
<th>Days from Adverse drug reaction to</th>
<th>Reporter</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-03-2006</td>
<td>15-07-2005</td>
<td>10-09-2005</td>
<td>201</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>01-12-2004</td>
<td>01-09-2005</td>
<td>210</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>29-06-2004</td>
<td>01-09-2004</td>
<td>575</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>05-12-2003</td>
<td>26-12-2003</td>
<td>825</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>08-01-2002</td>
<td>07-02-2002</td>
<td>1512</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>24-01-2006</td>
<td>01-02-2006</td>
<td>57</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>11-04-2005</td>
<td>11-05-2005</td>
<td>323</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>24-06-2005</td>
<td>03-08-2005</td>
<td>239</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>15-04-2005</td>
<td>22-04-2005</td>
<td>342</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>22-10-2004</td>
<td>02-12-2004</td>
<td>483</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>16-12-2002</td>
<td>16-01-2003</td>
<td>1169</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>17-08-2005</td>
<td>17-11-2005</td>
<td>133</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-03-2006</td>
<td>14-09-2005</td>
<td>14-11-2005</td>
<td>136</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>04-05-2006</td>
<td>18-01-2006</td>
<td>24-01-2006</td>
<td>100</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>10-05-2006</td>
<td>01-12-2005</td>
<td>19-12-2005</td>
<td>142</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>10-05-2006</td>
<td>08-08-2003</td>
<td>14-08-2003</td>
<td>1000</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>28-07-2006</td>
<td>18-09-2002</td>
<td>25-09-2002</td>
<td>1402</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>28-07-2006</td>
<td>01-12-2005</td>
<td>22-12-2005</td>
<td>218</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>10-11-2006</td>
<td>16-08-2005</td>
<td>07-09-2005</td>
<td>429</td>
<td>Holstebro Hospital</td>
</tr>
<tr>
<td>12-01-2007</td>
<td>21-12-2005</td>
<td>22-12-2005</td>
<td>386</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>30-10-2007</td>
<td>30-11-2005</td>
<td>02-12-2005</td>
<td>697</td>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>27-02-2008</td>
<td>15-03-2006</td>
<td>15-03-2006</td>
<td>714</td>
<td>Herlev Hospital</td>
</tr>
</tbody>
</table>
5.6.1. Distribution of Danish adverse drug reaction reports
As can be seen above the majority by far of reports concerning NSF and Omniscan® come from Herlev Hospital. The accumulation of cases of NSF at this hospital can be the result of the composition of the patient base and the amount of examinations performed. However, the overrepresentation and reported cases, specifically from Herlev Hospital, gives cause to consider other factors.
In continuation of section 5.2 about toxicology it must be emphasized that, for a number of years, Herlev Hospital apparently adhered to the practise of using Omniscan® for all patients with renal failure using the maximum dosis and in some cases, on more than one occasion despite the fact that many of the patients eliminated the compound extremely slowly.
Additionally, for a period of time, Herlev Hospital used MR-contrast examinations as a routine for patients with terminal renal failure. An increase in the method of examination could possibly have contributed to the increased incidence of NSF at this particular hospital.
Finally, section 9 shows that the consumption of Omniscan® at Herlev Hospital during the past 10 years has been bigger than in other hospitals. According to the Danish Medicines Agency’s information Skejby Sygehus has performed about 7,000 MR scanings over the past 12 years, of which 500 were on kidney patients with varying degrees of reduced renal function.
The investigation shows that three different contrast agents containing gadolinium, including Omniscan® were used, with a dosis of 0.1 mmol/kg b.w. as a basis (although somewhat more in the case of MR angiography, i.e. the examination of blood vessels). Only in exceptional cases were kidney patients examined more than once.
In a retrospective investigation of possible NSF patients from the renal units in Eastern Jutland (Århus, Randers and Horsens) it was only possible to identify one patient with NSF.

5.6.2. EMEA – The European Adverse Drug Reaction Database
On 11 March 2008 The European Adverse Drug Reaction Database had received 256 reports of NSF related to the use of the MR contrast preparations containing gadolinium. Most of the reports concern Omniscan®, second is Magnevist®. Both these products are now considered to be of high risk for the development of NSF. There are six reports regarding Optimark® (high risk reports are divided between five from the U.S. and 1 from Brazil) and one concerning Prohance® (medium risk).
The remaining 48 reports concern the use of two or more contrast agents for the same patients. The distribution of reports by product is shown in Table 2.

| Table 2. |
| Reports of NSF to The European Council for Adverse Drug Reactions (11 March 2008) |
| **Contrast agents with gadolinium numbers** |
| Omniscan® 120 |
| Magnevist® 81 |
| Omniscan® + Magnevist® 19 |
| Omniscan® + one or more other 8 |
| Omniscan® + one of more other (not Magnevist®) 11 |
Magnevist® + one or more other (not Omniscan®) 7
One or more products (neither Omniscan® nor Magnevist®) 10
In all 256

The first report was received in December 2004 and was from the U.S.
Up to 27 April 2006 there a further 13 reports, of which 9 were from Denmark and 3 from Austria. As per 1 February 2007 there were 112 registered reports: 63 from the U.S., 30 from Denmark, 12 from Germany and 3 from Austria.
The spread as per 11 March 2008 is shown in Table 3.

Table 3.

<table>
<thead>
<tr>
<th>Reports of NSF to The European Adverse Drug Reactions Database</th>
<th>Spread by country (11 March 2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country Number Reports</strong></td>
<td></td>
</tr>
<tr>
<td>USA 143</td>
<td></td>
</tr>
<tr>
<td>EU-countries 94</td>
<td></td>
</tr>
<tr>
<td>Switzerland 8</td>
<td></td>
</tr>
<tr>
<td>Canada 2</td>
<td></td>
</tr>
<tr>
<td>Norway 2</td>
<td></td>
</tr>
<tr>
<td>Japan 2</td>
<td></td>
</tr>
<tr>
<td>Singapore 2</td>
<td></td>
</tr>
<tr>
<td>Brazil 1</td>
<td></td>
</tr>
<tr>
<td>Taiwan 1</td>
<td></td>
</tr>
<tr>
<td>Unknown 1</td>
<td></td>
</tr>
<tr>
<td><strong>Total 256</strong></td>
<td></td>
</tr>
</tbody>
</table>

5.7. Periodic Safety Update Reports (PSUR)
The marketing authorisation holder of a drug must keep detailed records of all adverse reactions the company may, within reason, assume to have knowledge of, regardless of where in the world the adverse reactions occurred. The records shall be submitted to The Danish Medicines Agency as Periodic Safety Update Reports (PSUR).
The PSURs shall be sent to The Danish Medicines Agency at pre-determined dates. Furthermore, the marketing authorisation holder must prepare PSURS outside these dates, should The Danish Medicines Agency ask for it.

The Danish Medicines Agency has received a total of 18 PSURs regarding Omniscan®, since the product was authorised in Denmark in 1994. Hereafter is a brief mention of the three reports submitted around the time when Omniscan® was first linked to NSF. Additionally, the content of all the PSURs that were submitted up till the start of 2006 will be assessed in the light of the current knowledge of the link between Omniscan® and NSF.

5.7.1. PSUR – 1 February 2005 to 31 January 2006
From the PSUR that was submitted by the marketing authorisation holder for Omniscan® for the period 1 February 2005 to 31 January 2006 – i.e. just before the link between Omniscan® and NSF was known – that the product was sold in 93 countries and that an estimated 31.6 million patients been examined using the product.
During the period described in the PSUR 205 adverse drug reactions were reported, spread over 29 serious adverse drug reaction and 176 non-serious. Of the serious adverse drug reactions there were 8 unknown, i.e. not mentioned in the summary of product characteristics.
Since 1991, the marketing authorisation holder had received a total of 84 reports of serious, unknown adverse drug reactions in 69 patients. Only two of these cases are relevant in this present connection as they could have indicated NSF, see item 5.7.4.

5.7.2. PSUR – 1February to 15 March 2006
According to the PSUR for the period of 1 February to 15 May 2006 Omniscan® was sold in 94 countries and an estimated 33.4 million patients were examined using the product.
During that period the marketing authorisation holder received 81 reports of adverse drug reactions divided between 24 serious and 57 non serious.
When the PSUR was submitted to The Danish Medicines Agency the marketing authorisation holder knew of 26 reports of NSF (or NFD as the illness was previously named): 20 from Denmark, 5 from Austria and 1 from the U.S.

5.7.3. PSUR – 16 May 2006 to 31 January 2007
According to the PSUR for the period 16 May 2006 to 31 January 2007 Omniscan® was sold in 95 countries with an estimated 37.4 million patients examined with the use of the product.

During this period the marketing authorisation holder received 241 adverse drug reaction reports, 94 serious and 147 non-serious.
When the PSUR was submitted the marketing authorisation holder knew of 116 reports of NSF.

5.7.4. Assessment of PSURs till the beginning of 2006
Omniscan® was linked to NSF in the spring of 2006.
The Danish Medicines Agency has been through all PSURs for Omniscan® to this point. There are no indications in these PSURs, as to how the reports could have led to an earlier realisation of the link.
In the spring of 2006, more than 30 million patients had been examined with the use of Omniscan®, and until 31 January 2006 there were only two that concern – or may concern – NSF. The one is from 2002, but was originally reported as muscular pains and not till 2006 reclassified as NSF. It is uncertain whether the other concerns NSF but this cannot be excluded.

6. Sequence of Events 2006-2008

6.1. Report from Herlev Hospital, March-May 2006
On 16 March 2006 the Danish Medicines Agency was contacted by Peter Marckmann from the renal unit of Herlev Hospital regarding a suspicion that a total of 20 of the hospital's patients with
severely reduced renal function had experienced adverse drug reactions in the form of NSF after being MR scanned with the contrasts agent Omniscan®.

The Danish Medicines Agency informed Peter Marckmann about the obligation of medical practitioners to report adverse drug reactions and urged him to immediately report these adverse drug reactions. On 30 March 2006 the Danish Medicines Agency received 15 adverse drug reaction reports from Peter Marckmann.

Following an initial assessment in the Danish Medicines Agency the reports were forwarded to the marketing authorisation holder of Omniscan® as well as to EMEA and WHO in April 2006 – in accordance with the prevailing legislation.

On 4 May 2006 the Danish Medicines Agency received another adverse drug reaction report from Herlev Hospital and on 10 May a further four reports regarding patients at Herlev Hospital, but submitted by GE Healthcare.

6.2. Contact with companies and other authorities, May 2006

The Danish Medicines Agency summoned the marketing authorisation holder to a meeting about the issue on 11 May 2006. At this point in time, there were in all of the EU 25 known cases where NSF was a suspected adverse drug reaction to Omniscan®: On the one hand the 20 cases from Denmark mentioned above and the five cases from Austria.

At the meeting the Danish Medicines Agency directed that GE Healthcare prepare a PSUR regarding Omniscan® no later than by 2 June 2006.

On 11 May 2006 the Danish Medicines Agency also informed the authorities in the other EU countries about the issue and asked for information about possible adverse drug reaction reports regarding NSF from the countries’ adverse drug reaction databases.

The Danish Medicines Agency also brought the case to the EU Council for Adverse Drug Reaction. On 24 May 2006 the Danish Medicines Agency asked the other companies selling MR contrast agents with gadolinium in Denmark for a periodic safety update report for their respective products.

6.3. Announcement of a suspicion of adverse drug reaction to Omniscan®, May 2006

On 29 May 2006 – as the first authority in the EU – the Danish Medicines Agency warned the public about the suspicion of severe adverse drug reactions relating to the use of Omniscan® in kidney patients. The warning, which in accordance with normal practice was published on the homepage of The Danish Medicines Agency, reads:

"The Danish Medicines Agency has decided to investigate the safety of using the MR contrast agent Omniscan®, which contains gadolinium. This is a consequence of Danish medical practitioners having become suspicious about the possibility that Omniscan® can cause adverse drug reactions that they have not previously been aware of.

The supposed adverse drug reaction are increased development of connective tissue in the skin, which becomes thicker, more rough and hard. The condition is described as "nefrogen fibrosing dermopati" or "nefrogen systemic fibrosis", has only been observed in patients with severely reduced renal function."
The warning is attached as appendix 17. The Danish Medicines Agency was at that time also in touch with the American FDA that issued a warning the following month.

6.4. EU Adverse Drug Reaction Council, June 2006
In June 2006 the case was discussed for the first time in the EU Council for Adverse Drug Reaction. At this time 25 cases of the above mentioned cases of NSF as a possible adverse drug reaction to Omniscan® (20 from Denmark and five from Austria).

Part II added 1 April, 2008

The Adverse Drug Reaction Council was also aware of a register in the USA containing details of approx. 200 potential cases of NSF worldwide. However, one uncertainty with this register was that there was not a consensus regarding the criteria that should be met, before the diagnosis of NSF could be used. Neither was there, in all cases, reliable information as to the contrast agent given to the patients, the dose administered and whether a patient could have received several different contrast agents.

Compared with the information regarding the total use of Omniscan®, at that point in time, 30 million patients (worldwide) had been examined using the product, the number of adverse reaction incident reports was not alarming. Furthermore, it was also remarkable that there were only reports from 2 hospitals in the EU, even though Omniscan® had been used in a large number of hospitals throughout the EU for a number of years.

At the meeting, the general opinion was that it was highly unlikely that there was an association between Omniscan®/gadolinium and NSF. It also seemed even less likely that there could be a potential association could only be present for a single contrast agent out of the 8 contrast agents containing gadolinium that were on the market in the EU. Nevertheless, there was disagreement as to whether there was the need for a more in-depth study due to the nature of the adverse reactions. The study would include all contrast agents containing gadolinium and would either confirm or dismiss the suspicion of Omniscan®, as well as clarifying whether there were differences, with respect to risk, between Omniscan® and the other MRI contrast agents containing gadolinium. The Council was in agreement that as matters stood, there was no basis for action regarding Omniscan®, in the form of e.g. change suspension or revoking drug authorisation.

6.5. Follow-up with GE Healthcare, September – October, 2006
On September 20, 2006 the Danish Medicines Agency held yet another meeting with GE Healthcare. At this point in time they were aware of 48 cases of NSF
and were starting to follow up on reports of additional cases. At the meeting, GE Healthcare stated that it had sent letters to doctors in several countries, including Denmark. The company’s letter to the Danish doctors was sent August 4, 2006. The letter is attached as Appendix 18. It is normal practice, that a company sends out such letters to doctors (Dear doctor letter), when significant new information emerges regarding risks or adverse effects of a drug.

GE Healthcare also stated that Peter Marckmann from Herlev Hospital’s Department of Nephrology, had stated shortly before that the hospital did not wish to cooperate with the company in a study to further clarify the correlation between Omniscan® and NSF. It was agreed that GE Healthcare should send a draft text for the product summary on risks associated with the use of gadolinium-based contrast agents on patients with renal insufficiency.
Minutes from the meeting are attached as Appendix 19.

On October 23, 2006 GE Healthcare submitted a proposal for adding to the section regarding special warnings and rules of caution in the product overview for contrast agents containing gadolinium, so called class-labelling:
“Cases of Nephrogenic Fibrosing Dermopathy/Nephrogenic Systemic Fibrosis (NFD/NSF) have been reported in association with the use of gadolinium-based contrast agents in patients with severe renal insufficiency. Gadolinium-based contrast agents should be used cautiously in patients with severe renal insufficiency (eGFR <15-20 mL/min) only if the benefits clearly outweigh the risks.”
This statement was translated into Danish.

GE Healthcare was only prepared to add the warning to the product overview for Omniscan®, if the authorities imposed the same requirement for all of the other gadolinium-based contrast agents. However, there was no justification for this.

6.6. Danish Council for Adverse Drug Reactions (Bivirkningsrådet), September 2006
At a meeting of the Council for Adverse Drug Reactions on September 27, 2006, the Danish Medicines Agency provided an update regarding Omniscan, stating it was not documented that the occurrence of NSF in kidney patients examined using Omniscan®, was due to the contrast agent, but that adverse effect reports had resulted in the need for further studies.

At the meeting, the Danish Medicines Agency expressed that it could be problematic if, based upon the above, radiologists advised against the use of Omniscan® in kidney patients. It was also noted that doctors were generally unfamiliar with when and how to report adverse effects.

6.7. Workshop at Skejby Hospital, October 2006
On October 24, 2006, the MRI centre at Skejby Hospital held a workshop
with a view to sharing information and knowledge regarding the NSF situation in Western Denmark. Among the participants was Peter Marckmann, GE Healthcare, Bayer Schering Pharma (marketing authorisation holder the contrast agent Magnevist®) and the Danish Medicines Agency. At the meeting, it was evident that doctors from the Department of Nephrology at Skejby Sygehus believed it was unlikely that there was a general association between gadolinium and NSF as they, despite the widespread use of Omniscan® and other gadolinium-based contrast agents, had not seen a single case of NSF. Doctors from Skejby Sygehus assumed that special conditions at Herlev Hospital must come into play. Consultant Hans Erik Hansen from Skejby Sygehus also did not recognise the alarming statements that had come from Herlev Hospital just a few months before. Following the workshop, on October 31, 2006, Skejby Sygehus published an article on Sundhed.dk about "MR scanning using contrast agents on patients with severe renal insufficiency". The following appeared in the article, "Danish radiology departments, including that at Skejby Sygehus, took on board the consequences of the new information and made a change in practice, among others, when referring patients with severe renal insufficiency to other modalities or the use of alternative gadolinium-based contrast agents. In addition, studies have also been performed at a large number of similar radiological MR centres and nephrology department, however, it is striking that similar cases of NSF have yet to be documented at other Danish hospitals. At Skejby Hospital we have, for a number of years, treated the same patient group as Herlev Sygehus using the same contrast agents without being able to show a single case of NSF. This fact is a very good basis for further studies with a view to finding the causal relationship with NSF."

The article from Sundhed.dk is attached as Appendix 20. 36

6.8. EU Adverse Drug Reaction Council, November 2006
Result of the EU Adverse Drug Reaction Council’s study, which was primarily based upon safety update reports concerning the gadolinium-based contrast agents that were on the market in the EU, was available in November 2006. Apart from a very few cases, where NSF possibly was an adverse effect of the product Magnevist®, suspicion was concentrated around Omniscan®. There were a total of 48 reports of NSF as an adverse effect of Omniscan®, while a further 40 reports were being assessed. EU Adverse Drug Reaction Council decided to see expert advice with a view to clarifying whether the physical-chemical qualities or stability of gadolinium-based contrast agents could explain the occurrence of NSF, including differences between the products and the correlation between these differences, as well as the emergence of adverse effect reports.

6.9. The EU P EU Adverse Drug Reaction Council, January 2007
At a meeting on January 22, 2007, the EU Adverse Drug Reaction Council evaluated the information regarding NSF and gadolinium that was available at that point in time. Henrik
Thomsen was invited to the meeting as an expert in the field. According to Henrik Thomsen, there were 55 cases of NSF following the use of Omniscan® in the scientific literature, of these 13 were from Denmark, 5 from Austria, 2 from Belgium and 35 from the USA. In addition to these, there were also a few cases linked to a couple other products, namely Magnevist® and Optimark®. In addition to the studies mentioned in section 5, the EU Adverse Drug Reaction Council was aware of, at that point in time, one additional study that had not yet been published (It was published later in 2007). The study showed that among 301 dialysis patients who had received Omniscan®, there were 12 cases of NSF. In comparison, there were no cases of NSF among 258 dialysis patients who had not received Omniscan®. The study also showed that the risk was significantly higher if a dose of 0.2 mmol/kg bodyweight was used rather than with the use of 0.1 mmol/kg.

Based upon the existing material, including the adverse effect reports, published and non-published studies, expert opinions, etc. a picture was painted that showed a clear connection between the use of Omniscan® and the occurrence of NSF. There was also a plausible scientifically substantiated explanation as to why there was a connection pieced together by hypotheses about transmetallation, gadolinium accumulation in the skin and stimulation of connective tissue formation, cf. sections 5.2 and 5.5.

The EU Adverse Drug Reaction Council decided to advise against the use of Omniscan® on patients with renal insufficiency. In February 2007, the Danish Medicines Agency changed the product summary for Omniscan® accordingly, cf. section 4.2.7. For all other gadolinium-based contrast agents, the EU Adverse Drug Reaction Council decided that the product summary should state caution should be exercises when using medicinal products on kidney patients. This recommendation was also incorporated immediately by the Danish Medicines Agency into Danish product summaries for the nationally approved products (Dotarem®: February 28, 2007, Prohance ® March 7, 2007 and Magnevist® March 7, 2007).

The other gadolinium-based contrast agents are either approved in the mutual recognition procedure or centrally approved. Here, the respective reference countries or EMEA have incorporated changes in the product summary.

As a follow-up to the EU Adverse Drug Reaction Council’s evaluations, recommendations and the immediate change made thereafter on the product summary for Omniscan®, the Danish Medicines Agency issues new recommendations on February 7, 2007 for the use of MR contrast agents on kidney patients. The recommendations specified, among others, that Omniscan® should not be used on patients with severe renal failure and that children up to the age of 1 should only be examined with Omniscan® following careful consideration. The recommendations published on the Danish Medicines Agency website are located in Appendix 21.

6.11.1. NSF in persons with moderate renal insufficiency At the EU Adverse Drug Reaction Council meeting on February 19-21, 2007 it was decided that a warning should be added to the Omniscan® product overview that cases of NSF have been seen in patients with moderate renal insufficiency. The precise wording was subsequently established by the Swedish Medical Products Agency (MPA). The product summary was changed in accordance with the above on June 28, 2007, cf. section 4.2.7.

6.11.2 Magnevist® and other gadolinium-based contrast agents
In March 2007, new information emerged regarding the contrast agent Magnevist®. 42 cases of NSF had been identified in patients who were examined using Magnevist®, partly publicised in a so-called abstract in 2006, partly received as adverse effect reports (not from Denmark). This is highly consistent with Magnevist®, with respect to the physical-chemical properties and structure similar to Omniscan® Pre-clinical studies did not indicate the presence of NSF-like skin changes in rats following administration of Magnevist®, as opposed to following administration of Omniscan®. Based upon this, the EU Adverse Drug Reaction Council decided on March 19, 2007 to advise against the use of Magnevist® in patients with severe renal insufficiency. It was also decided that holders of the licenses to market other linear gadolinium-based MRI contrast agents (Multihance®, Primovist® and Vasovist®) must submit a explanatory statement explaining why a similar contraindication should not be introduced for these products.

In April 2007, marketing authorisation holder Magnevist®, Bayer Schering Pharma, rejected the addition of a contraindication concerning use in patients with severe renal insufficiency. The company stated this was because the risk of NSF was related to the use of dosages that were greater than what was approved (appeared in the product summary) for Magnevist®.

6.11.3. Gadolinium and transmetallation
At a meeting on May 21-23, 2007 the EU Adverse Drug Reaction Council evaluated a completely new study focusing on the transmetallation process. This study compared the physical and chemical properties of 6 gadolinium-based MR contrast agents: Omniscan®, Magnevist® and Multihance® (linear), in addition to Dotarem®, Prohance® and Gadovist® (cyclical). The study showed that transmetallation happened fastest and was the most disseminated following the use of Omniscan® and second fastest following the use of Magnevist®. Multihance®, which underwent a significantly slower and less disseminated transmetallation. Unlike the above, the three cyclical products were particularly stable, i.e. had a particularly slow exploitation of gadolinium ions. Thus, additional material existed that supported the correlation between Magnevist® and NSF.
The EU Adverse Drug Reaction Council, upheld the decision that a contraindication should be added to the product information for Magnevist®. The wording was available in June 2007 and was added to the product information on January 22, 2008.

6.11.4. Contraindication for gadolinium-based linear contrast agents
Based upon the information amassed, the EU Adverse Drug Reaction Council, at its meeting from June 23-25, 2007, decided that product information for the other linear, gadolinium-based MR contrast agents, Multihance®, Vasovist® and Primovist®, should have a contraindication added concerning patients with severe renal insufficiency. However, the holders of the licenses to market Multihance®, Vasovist® and Primovist® rejected the addition of a contraindication to their product information. The EU Adverse Drug Reaction Council then decided to consult the EMEA’s Scientific Advice Group for Diagnostics, who at a meeting on December 3, 2007 evaluated a number of concrete questions. Participating in the meeting were representatives from the EU Committee for Medicinal Products for Human Use (CHMP) and the EU Adverse Drug Reaction Council, in addition to external experts, among these Henrik Thomsen.

EMEA’s Scientific Advice Group for Diagnostics concluded that, among others:

• Gadolinium-based contrast agents can be divided into 3 risk groups with respect to NSF.
  High risk: Omniscan® and Magnevist®.
  Medium risk: Multihance®, Vasovist® and Primovist®.
  Low risk: Dotarem®, Prohance® and Gadovist®.
• The cyclical products, i.e. the three low risk products can be used on patients with severe renal insufficiency when MR scanning is obviously the best examination method.
• Contraindication of the use of all gadolinium-based MR contrast agents on renal patients is not recommended, as in certain cases there are no alternatives
• The product information wording for Multihance®, Vasovist® and Primovist® (medium risk) is sufficient There is no basis for introducing a contraindication. The changes that have already been made to the product information are sufficient.
• There is a need for further studies in certain areas, for example, long-term effects of the use of gadolinium, including the potential risks in association with the accumulation of gadolinium in bone tissue, developing a suitable animal model for renal insufficiency and improved MR techniques.

6.11.5. Comments from GE Healthcare
On February 29, 2008 the Danish Medicines Agency asked the marketing authorisation holder for Omniscan®, GE Healthcare, to comment on the press coverage of Omniscan® in the media, particularly Dagens Medicin, including allegations that the company had withheld or misrepresented important safety information. GE Healthcare has, in its letter dated March 13, 2008, forwarded its comments. The letter is attached as Appendix 22.
7. Risks to persons with normal renal function

Until now, the general consensus is that gadolinium-based contrast agents are regarded as safe to patients with normal renal function. For example, Henrik Thomsen wrote the following in European Radiology in autumn 2006 (this statement was translated into Danish):

“There are no reports of NSF in patients with normal renal function. Approximately 200 million patients have been injected with contrast agents containing gadolinium since the start of the 1980’s. More than 30 million patients have received gadodiamide. All gadolinium-based contrast agents should therefore be assumed as being safe for use in patients who do not have renal insufficiency”. The article is attached as Appendix 23.

In an article in Dagens Medicin on February 29, 2008, a question was raised as to whether it is only persons with renal insufficiency who risk developing NSF after being examined using Omniscan®.

The article puts forward that persons without renal insufficiency also risk gadolinium poisoning because the substance can be stored in the bones. When or if the substance is later released from the bones, it may pose a severe health risk. According to Dagens Medicin, Henrik Thomsen from Herlev Hospital fears that the relatively few renal patients who have developed NSF due to Omniscan® are only “the tip of the iceberg”, with respect to the risk for gadolinium poisoning.

Henrik Thomsen is cited in the article for, among others, this statement: “Free gadolinium is also concentrated in the bones of patients with normal renal function. Following each MR examination using Omniscan®, a small quantity of gadolinium binds to the bone tissue in the patient, where it remains for many years. My worry is what will happen when the gadolinium is released from the bone tissue”.

Gadolinium can be found in tissue samples (skin biopsies) from renal patients who have developed NSF after being examined using a gadolinium-based contrast agent. This has been proven by several researchers, most recently Peter Marckmann, who has also proven that the content of gadolinium rises in tissue samples from renal patients taken over a certain period of time after an MR scan. This finding has led to the theory that gadolinium accumulates in patient bone tissue, from which it is gradually released and leads to the development of NSF. According to Peter Marckmann, however, no studies have been published documenting that gadolinium is released from the bone tissue of patients with NSF.

The Danish Medicines Agency is not aware of data, including adverse effect reports, showing that the use of Omniscan® in persons with normal functioning kidneys involves a risk of developing NSF. Millions of patients around the world, most with normal renal function, have received gadolinium-based contrast agents over the years. Still, there are no reports of NSF in persons with normal renal function. Nonetheless, it is the Danish Medicine Agency’s opinion that there is
a problem that deserves a more in-depth study. However, this falls outside of the parameters of this report.

8. Change, suspension or revocation of an authorisation
Under certain conditions, the Danish Medicines Agency can change, suspend or revoke authorisation of a drug. The conditions appear in The Danish Medicines Act, §§ 14-16. Among the most important conditions are:
• The benefit-risk ratio is not favourable
• Essential information stated by the applicant in support of the marketing authorisation application proves to be incorrect
• The marketing authorisation holder has failed to take into account new information about the technical and scientific development
• The marketing authorisation holder has failed to inform the Danish Medicines Agency of new information about the relationship between the benefits and risks afforded by the medicinal product in accordance with the Danish Medicine Act § 25, section 1.

The choice between change, suspension and revocation of the marketing authorisation shall be based upon the proportionality principle, i.e. the reaction may not be more radical than necessary. The Danish Medicines Agency can only revoke a marketing authorisation it has issued. If the matter relates to a centrally approved drug, the marketing authorisation is issued by the EU and, therefore, only the EU can revoke it. However, if it is necessary to act fast in order to protect human or animal health or the environment, the Danish Medicines Agency can suspend the use of a centrally approved drug here in the country, cf. article 20 section 4, in regulation no. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency Suspension or revocation of a marketing authorisation can only occur, if there is new information. The Danish Medicines Agency is obliged to ensure that the information is correct and valid before making such a decision. The Danish Medicines Agency cannot, within the framework of current legislation, suspend or revoke a marketing authorisation solely because a doctor or researcher raises suspicion that, for example, a drug has serious adverse effects that were unknown until now.

The background as to why the Danish Medicines Agency cannot suspend or revoke authorisation of a drug out of hand is, partly out of consideration for the company that has the drug on the market and partly to the patients who benefit from the drug.

Authorisation of a drug is in administrative law terms, a preferential, i.e. a decision that gives the recipient certain rights, here the right to sell a drug. A preferential administrative act cannot be freely changed or revoked by the issuing authority. If the legislation, which the decision is issued in pursuance of, expressly specifies the reasons that can lead to change, suspension or revocation of a decision, one can normally conclude per contra that it may not take place for any reason other than the reasons specified.
The Danish Medicines Act as mentioned in the regulations above that expressly state when authorisation of a drug can be changed, suspended or revoked. Drugs are used to diagnose, prevent and treat diseases. If the marketing authorisation of a drug is suspended or revoked, it not only means that the risk of any adverse effects when using the precise drug in question are eliminated, but also that patients who use and benefit from the drug are deprived of an opportunity for treatment. Weighing the benefits over the risks is a central element in authorisation and monitoring of drugs, and thus each risk cannot be grounds for withdrawal of a drug from the market.

In many situations where new knowledge, or doubt, emerges about the risks of a certain drug, it will be more relevant to disclose the new knowledge so that doctors can take it into consideration when they choose a treatment for their patients and so that their patients are informed of these risks, rather than suspension or revoking authorisation of the drug.

8.1. Evaluation of Omniscan®
As stated in section 6.1, in spring 2006 the Danish Medicines Agency received 20 reports of the severe adverse effect NSF in association with the use of Omniscan®. In evaluating whether these reports could substantiate an immediate suspension of the authorisation of Omniscan®, the Danish Medicines Agency weighed the following:
- Almost all of the reports came from one hospital
- In all of the reported cases, there was talk of adverse effects in connection with the use of the contrast agent on a well defined patient group, namely patients with severely impaired renal function.
- Despite Omniscan® having been on the market since the start of the 1990’s and having been used by more than 30 million patients, on a global level there was a very limited number of cases of NSF that were suspected to be an adverse effect of Omniscan®, including 25 within the EU (of these 20 from Denmark).

Based upon this, the Danish Medicines Agency deemed that the relationship between the benefits and risks generally had not moved from favourable to unfavourable, cf. the Danish Medicine Act § 14, section 1 no. 1. Therefore, there were no grounds for immediately changing, suspending or revoking authorisation of Omniscan®. However, the Danish Medicines Agency decided to publicise the suspicion that had been raised, among others, with a view to increasing doctor attention surrounding the use of Omniscan® in persons with renal insufficiency. The information was made public on May 29, 2006.

As more closely described in section 6, the Danish Medicines Agency, in line with the EU Adverse Drug Reaction Council and the other EU authorities, also did not following a closer investigation of the risks associated with the use of Omniscan®, find a basis for suspending or revoking authorisation of the product. On the other hand, the product information was changed so that the use of the drug on patients with renal insufficiency was now expressly

9. Use of Omniscan® in Denmark
During 1997-2007, there have been 17 different Omniscan® packs (ATC code V08CA03) on the Danish market (table 4).

| Table 4. Omniscan® packs on the market during 1997-2007 |
|-----------------|-----------------|-----------------|-----------------|
| **Product number** | **Pack** | **Ml in total** | **Strength** | **Mmol in total** |
| 074443 | 10 htgl. containing 5 ml | 50 | 0.5 mmol/ml | 25 |
| 160408 | 10 x 10 ml | 100 | 0.5 mmol/ml | 50 |
| 160457 | 10 x 15 ml | 150 | 0.5 mmol/ml | 75 |
| 160622 | 10 x 20 ml | 200 | 0.5 mmol/ml | 100 |
| 165662 | 10 htgl. containing 10 ml | 100 | 0.5 mmol/ml | 50 |
| 165670 | 10 htgl. containing 15 ml | 150 | 0.5 mmol/ml | 75 |
| 165878 | 10 htgl. containing 20 ml | 200 | 0.5 mmol/ml | 100 |
| 165894 | 10 x 50 ml | 500 | 0.5 mmol/ml | 250 |
| 191833 | 10 htgl. containing 10 ml | 100 | 0.5 mmol/ml | 50 |
| 191858 | 10 htgl. x 15 ml | 150 | 0.5 mmol/ml | 75 |
| 191908 | 10 htgl. x 20 ml | 200 | 0.5 mmol/ml | 100 |
| 466326 | 10 x 10 ml pre-filled syringes | 100 | 0.5 mmol/ml | 50 |
| 466573 | 10 x 15 ml pre-filled syringes | 150 | 0.5 mmol/ml | 75 |
| 466714 | 10 x 20 ml pre-filled syringes | 200 | 0.5 mmol/ml | 50 |
| 490656 | 10 x 10 ml | 100 | 0.5 mmol/ml | 50 |
| 490680 | 10 x 15 ml | 150 | 0.5 mmol/ml | 75 |
| 490706 | 10 x 20 ml | 200 | 0.5 mmol/ml | 100 |

The quantity sold is calculated in mmol/substance, because Omniscan® has not been allocated the WHO’s quantity unit DDD (Defined Daily Dose). Based upon the quantity sold, a dose of 0.1 mmol/kg body weight and the assumption that an average patient weighs 70 kg (weight used by WHO to establish a DDD), it can be estimated that Omniscan® has been used in 3,000-17,000 "standard treatments" annually during the period between 1997-2007 (table 5).

Use peaked during the period between 2003-2006 with 10,000 to 17,000 "standard treatments" annually.
Table 5. Quantity of Omniscan® sold and number of “standard treatments”* calculate (0.1 
mmol/kg body weight for a patient of 70 kg)

<table>
<thead>
<tr>
<th>År</th>
<th>Sygehussektor</th>
<th>Primærsektor</th>
<th>I alt</th>
<th>Sygehussektor</th>
<th>Primærsektor</th>
<th>I alt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mmol</td>
<td></td>
<td></td>
<td>Standardbehandlinger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>23.075</td>
<td></td>
<td>23.075</td>
<td>3.296</td>
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<td>3.296</td>
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<tr>
<td>1998</td>
<td>32.625</td>
<td></td>
<td>32.625</td>
<td>4.661</td>
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<td>4.661</td>
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<tr>
<td>1999</td>
<td>29.875</td>
<td></td>
<td>29.875</td>
<td>4.268</td>
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<td>4.268</td>
</tr>
<tr>
<td>2001</td>
<td>57.200</td>
<td></td>
<td>57.200</td>
<td>8.171</td>
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<tr>
<td>2002</td>
<td>64.875</td>
<td></td>
<td>64.875</td>
<td>9.268</td>
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<td>9.268</td>
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<tr>
<td>2003</td>
<td>71.525</td>
<td>400</td>
<td>71.582</td>
<td>10.218</td>
<td>57</td>
<td>10.275</td>
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<tr>
<td>2004</td>
<td>96.200</td>
<td>150</td>
<td>96.221</td>
<td>13.743</td>
<td>21</td>
<td>13.764</td>
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<tr>
<td>2005</td>
<td>117.325</td>
<td>3.600</td>
<td>117.839</td>
<td>16.761</td>
<td>514</td>
<td>17.275</td>
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<td>2006</td>
<td>78.475</td>
<td>2.625</td>
<td>78.850</td>
<td>11.211</td>
<td>375</td>
<td>11.586</td>
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<tr>
<td>2007</td>
<td>27.950</td>
<td>325</td>
<td>27.996</td>
<td>3.993</td>
<td>46</td>
<td>4.039</td>
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<tr>
<td>I alt</td>
<td></td>
<td></td>
<td></td>
<td>91.193</td>
<td>1.014</td>
<td>92.207</td>
</tr>
</tbody>
</table>

On an annual basis, the hospital sector has stood for 97-100 percent of the consumption. In table 
6, consumption is shown by hospital based upon the hospital classification from December 2007 
and in table 7, consumption is shown distributed by prescription issuers in the primary 
healthcare sector.

38 hospitals have used Omniscan® during the studied period. Herlev Hospital 
stands out as it has used more than 3 times as much as Åbenrå Sygehus, which used the second 
most. A pronounced drop in consumption is shown in most hospitals from 2006 to 2007.

Omniscan® has, in few cases, been sold at private chemists with a view to 
being used in private clinics or at private hospitals (table 7). 
When making calculations based upon standard treatments, due to the nature of the matter, it 
has not been taken into account that in some situations other 
quantities and higher doses are used. Therefore, the number of standard treatments is solely an 
estimate of the level of the number of patients treated and an expression of the maximum 
number of patients that may have been examined. For example, it seems that a higher dose was 
generally used at Herlev Hospital than at Skejby Sygehus, which is why the actual difference 
between the numbers of treatments at these two hospitals is less than indicated in table 6.
<table>
<thead>
<tr>
<th>Tabell 6. Beregnet antal &quot;standardbehandlinger&quot; fordelt på sygehuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-2001</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Herlev Hospital</td>
</tr>
<tr>
<td>Sygehus, Aalborg</td>
</tr>
<tr>
<td>Vejle Sygehus</td>
</tr>
<tr>
<td>Roskilde Sygehus</td>
</tr>
<tr>
<td>Århus Universitetshospital, Skejby</td>
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<td>Aalborg Sygehus</td>
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<td>Sygehus, Randersborg</td>
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<tr>
<td>Gistrup Hospital</td>
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<td>Odense Universitetshospital</td>
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<tr>
<td>Århus Sygehus</td>
</tr>
<tr>
<td>Regionshospital, Holstebro</td>
</tr>
<tr>
<td>Nordsjællands Hospital</td>
</tr>
<tr>
<td>Frederiksborg Hospital</td>
</tr>
<tr>
<td>Sygehus, Aarhus</td>
</tr>
<tr>
<td>Regionshospital, Viborg</td>
</tr>
<tr>
<td>Sygehus, Vendsyssel</td>
</tr>
<tr>
<td>Sygehus, Middelfart</td>
</tr>
<tr>
<td>Gentofte Hospital</td>
</tr>
<tr>
<td>Hillerød Sygehus</td>
</tr>
<tr>
<td>Syddjurs Sygehus</td>
</tr>
<tr>
<td>Stormiddemølt Sygehus</td>
</tr>
<tr>
<td>Centralsygehuset i Nykøbing F.</td>
</tr>
<tr>
<td>Regionshospital, Herning</td>
</tr>
<tr>
<td>Righospitalet</td>
</tr>
<tr>
<td>Hvidovre Hospital</td>
</tr>
<tr>
<td>Herlev, Brodbus, Odder Hosp.</td>
</tr>
<tr>
<td>Centralsygehuset i Næstved</td>
</tr>
<tr>
<td>Kong Chr. IXs Gigthospital, græsten</td>
</tr>
<tr>
<td>Giv sygehus</td>
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<tr>
<td>Kong Sygehus</td>
</tr>
<tr>
<td>Privathospitalet Hørsholm</td>
</tr>
<tr>
<td>Fredericia Og Holbæk Sygehus</td>
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<td>Holbæk Sygehus</td>
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<td>Sygehus, Fyn</td>
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<td>Sygehus, Fyn Region</td>
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Table 7. Primary healthcare sector. Estimated number of "standard treatments" dispensed by private chemists, divided by prescription issuer

<table>
<thead>
<tr>
<th>Receptudsteder</th>
<th>By</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>I alt</th>
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<tr>
<td>Læge på Hamlet</td>
<td>Frederiksborg</td>
<td>236</td>
<td>250</td>
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<td></td>
<td></td>
<td>486</td>
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<tr>
<td>Læge på Røntgenklinikken ApS</td>
<td>Århus C</td>
<td>64</td>
<td>86</td>
<td>39</td>
<td></td>
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<td>189</td>
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<tr>
<td>Kan ikke bestemmes</td>
<td></td>
<td>143</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>147</td>
</tr>
<tr>
<td>Kan ikke bestemmes</td>
<td></td>
<td>71</td>
<td>29</td>
<td>7</td>
<td></td>
<td></td>
<td>107</td>
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<tr>
<td>Kan ikke bestemmes</td>
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<td>57</td>
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</tr>
<tr>
<td>Kan ikke bestemmes</td>
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<td></td>
<td></td>
<td></td>
<td>21</td>
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<tr>
<td>Læge på Haslev Lægecenter</td>
<td>Haslev</td>
<td>7</td>
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