CASE AUTH/2169/9/08

GE HEALTHCARE v BRACCO

Promotion of Niopam

GE Healthcare complained about the promotion of Niopam by Bracco using the IMPACT study (Barrett *et al* 2006) and alleged that pertinent information about its conduct, design and analysis had been omitted.

The study, entitled 'Contrast-Induced Nephropathy in Patients with Chronic Kidney Disease undergoing Computed Tomography: A double-blind comparison of Iodixanol and Iopamidol' aimed to 'prospectively compare the incidence of CIN [contrast induced neuropathy] after intravenous injection of equi-iodine doses of iopamidol-370 and iodixanol-320'.

A Bracco-sponsored webcast by one of the study's authors, described the IMPACT study as 'prospective, multi-centre, double-blind, randomised parallel groups'. Leavepieces also sought to imply the prospective, randomised, controlled nature of this study.

The study was in fact the combination of data from two separate Bracco studies, VIRPACT and INVICTA. Contrary to the impression portrayed by the publication and the promotional materials, neither of these studies examined CIN as their primary endpoint. The primary objective of INVICTA was to examine image quality in patients undergoing peripheral vascular imaging with either iopamidol-370 or iodixanol-320. The primary objective of VIRPACT was to examine image quality in patients undergoing liver multidetector-row CT with either iopamidol-370 or iodixanol-320. Both studies had a secondary objective of examining CIN rates. These studies were only combined after patient recruitment was stopped, treatment and assessment were complete and statistical analyses underway and after the overall CIN rates of these studies could easily have been known.

GE Healthcare believed that neither the original publication nor promotional materials or activities stemming from this study accurately depicted its conduct. Additionally, the decision to combine data post-hoc, subsequent to collection of data endpoints and commencement of statistical analysis was of questionable validity. This breached the principles underpinning the conduct of clinical studies and brought discredit to the industry.

GE Healthcare alleged that Bracco's promotional materials omitted critical information on the conduct of the study, and were misleading and incapable of substantiation. Bracco's failure to maintain high standards breached the Code and risked bringing discredit to the industry in breach of Clause 2.

These concerns had been raised in inter-company correspondence, Bracco did not contest that IMPACT had pooled data from two earlier study protocols, one that had completed enrolment and the other that had been stopped. Rather it claimed that IMPACT was a prospective, multi-centre, double-blind, randomised, parallel group study which followed the best of clinical practice guidelines. GE Healthcare disagreed, as the IMPACT protocol was developed after patient enrolment had been completed, and after the patient data had been collected and a blinded analysis had been conducted.

The detailed response from Bracco is given below.

Certain of the allegations were not considered by the Panel because they had not been the subject of intercompany dialogue.

The Panel noted that the study concluded that the rate of CIN in patients with moderate-to-severe chronic kidney disease was similarly low after intravenous administration of equi-iodine doses (40g) of iopamidol-370 or iodixanol-320 for contrast-enhanced multi-detector computed tomography. The materials and methods section discussed the study patients, protocol and statistical analysis. It appeared to be one study designed *de novo* to assess the primary outcome measure. The discussion section stated that the results of the trial failed to demonstrate any difference in the incidence of CIN between equi-iodine doses of iodixanol-320 and iopamidol-370 for IV use in patients with pre-existing stable chronically reduced kidney function. The study authors noted that this was at odds with the findings of a previous trial comparing a nonionic monomer, iohexol with iodixanol but consistent with findings in other prospective or retrospective studies. It was noted that several previous studies had weaknesses which detracted from the IMPACT study authors' ability to reach valid conclusions. The study authors then described IMPACT as the largest prospective, randomized, double-blind comparison of iodixanol with a non-ionic monomer. Study limitations were discussed including calculation of the sample size which was based on the apparent differences between contrast agents in the NEPHRIC study (Aspelin *et al*, 2003). Whilst the number of subjects in IMPACT was higher (153 vs 129) the incidence of CIN observed was lower than anticipated. The IMPACT study authors noted that with the CIN incidence rates in the trial a study of about 3,800 cases would be required to detect even a 50% reduction in the incidence of CIN with one contrast medium over the other.

The Panel noted Bracco's submission that the prospective defining of patients, data and endpoints was entirely proper and the failure to mention the protocol amendments combining the data in, *inter alia*, related promotional material was completely irrelevant and would not affect readers' perception of the IMPACT data. The safety objectives and endpoints were the same in both studies. An expert on the Renal Safety Data Monitoring Board established by the IMPACT protocol confirmed that the board undertook a blinded review of data from INVICTA and VIRPACT to make the required determinations including eligibility. CIN rates were not known until the blind was broken for statistical analysis when the data from the two studies was combined. The protocols were identical with respect to CIN. There were no cases of CIN following iopamidol in either study; all of the very few cases of CIN occurred after iodixanol.

The Panel noted that GE Healthcare had provided a booklet entitled 'The Care Pathway Managing the Chronic Kidney Disease Patient in the Cardiology and Radiology Department'. A page headed 'Latest Clinical Evidence: The IMPACT Study' outlined the methodology from the published study and depicted the results in two bar charts. The first showed the percentage of patients with an increase in serum creatinine ≥ 0.5mg/dL from baseline (iopamidol-370, 0%, iodixanol-320, 2.6%; p=0.30). The second showed the percentage of patients with an increase in serum creatinine ≥25% from baseline (iopamidol-370, 3.9%, iodixanol, 4%; p=0.4). An asterisked statement beneath the bar charts read 'The observed differences in CIN rates were not statistically significant (p>0.05)'. The Panel was concerned that the first bar chart gave the immediate visual impression of a statistically significant difference between the products whereas the study failed to demonstrate a difference.

The Panel noted that promotional material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and queried whether the reader had been provided with sufficient information about the study methodology to enable them to decide how much weight to attach to the data.

The Panel noted that the secondary endpoint data from two separate studies had been combined to become the primary endpoint in the IMPACT study. The material gave the impression that the CIN data was originally derived from a study wherein it was a primary endpoint. That was not so. The position was more complicated. The Panel also queried whether the study was sufficiently powered to detect a statistically significant difference. The Panel considered that on balance the failure to provide more information about the study methodology and sample size was a material omission and was misleading. A breach of the Code was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

GE Healthcare had also provided a branded summary of the study. This reproduced the data shown in bar charts referred to above and on a key message page stated 'The results showed a low level of CIN, with no significant difference observed between the two contrast agents'. The Panel queried whether stating that there was no significant difference observed between the products fairly reflected the fact that the study failed to demonstrate a difference between the products bearing in mind the authors' comments about the low incidence of CIN and that given this a study of about 3,800 would be required to detect a 50% reduction in the incidence of CIN. The Panel considered that its comments above also applied to the study summary. The Panel considered that on the balance of probabilities the omission of pertinent information was misleading as alleged. A breach of the Code was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

GE Healthcare complained about the promotion of Niopam (iopamidol) by Bracco UK Ltd. GE Healthcare marketed Visipaque (iodixanol)

COMPLAINT

GE Healthcare complained about the promotion of Niopam using the IMPACT study (Barrett *et al* 2006) and alleged that pertinent information about the conduct, design and analysis of this study had been omitted.

This study, entitled 'Contrast-Induced Nephropathy in Patients with Chronic Kidney Disease undergoing Computed Tomography: A double-blind comparison of Iodixanol and Iopamidol', was published in Investigative Radiology in 2006. The aim of the study was to 'prospectively compare the incidence of CIN [contrast induced neuropathy] after intravenous injection of equi-iodine doses of iopamidol-370 and iodixanol-320'.

A variety of materials from Bracco pursued this theme. For example, in a Bracco-sponsored webcast by one of the study's authors, the design of the IMPACT study was described as 'prospective, multi-centre, double-blind, randomised parallel groups'. Similarly, promotional materials such as leavepieces also sought to imply the prospective, randomised, controlled nature of this study.

IMPACT investigators had provided evidence that the study was in fact the combination of data from two separate Bracco studies, VIRPACT and INVICTA. Of significance, and contrary to the impression portrayed by the publication and the promotional materials, neither of these studies examined CIN as their primary endpoint. The primary objective of INVICTA was to examine image quality in patients undergoing peripheral

vascular imaging with either iopamidol-370 or iodixanol-320. The primary objective of VIRPACT was to examine image quality in patients undergoing liver multidetector-row CT with either iopamidol-370 or iodixanol-320. Both studies had a secondary objective of examining CIN rates. These studies were only combined after patient recruitment was stopped, treatment and assessment were complete and statistical analyses underway and after the overall CIN rates of these studies could easily have been known.

GE Healthcare believed that neither the original publication nor promotional materials or activities stemming from this study accurately depicted its conduct. Additionally, the decision to combine data post-hoc, subsequent to collection of data endpoints and commencement of statistical analysis was of questionable validity. Such actions breached the principles underpinning the conduct of clinical studies and brought discredit to the industry.

GE Healthcare alleged that Bracco's promotional materials omitted critical information on the conduct of this study, and therefore were misleading, incapable of substantiation in breach of Clauses 7.2, 7.4 and 7.10 of the Code. Furthermore, in this respect, Bracco's failure to maintain high standards breached Clause 9.1 and risked bringing discredit to the industry in breach of Clause 2.

These concerns had been raised in inter-company correspondence, Bracco did not contest that IMPACT had pooled data from two earlier study protocols, one that had completed enrolment and the other that had been stopped. Rather it claimed that IMPACT was a prospective, multi-centre, double-blind, randomised, parallel group study which followed the best of clinical practice guidelines. GE Healthcare disagreed, as the IMPACT protocol was developed after patient enrolment had been completed, and after the patient data had been collected and a blinded analysis had been conducted.

As it was unlikely that it would resolve this matter, GE Healthcare therefore deferred to the Authority for assistance. It asked that materials relating to IMPACT be withdrawn and that Bracco be required to communicate the material information that was omitted on the conduct of the study to the editorial board of Investigative Radiology and to clinicians with whom these data had been shared.

RESPONSE

Bracco stated that the allegations were groundless and false. It showed below and in an accompanying statement from an expert on the Renal Safety Data Monitoring Board established by the IMPACT protocol that IMPACT was a valid, prospective study that was conducted appropriately.

Bracco stated that it first learned of GE Healthcare's intention to submit the complaint from a letter of 28 August that alleged, without any basis, that the IMPACT promotion was improper. In response, Bracco asked GE Healthcare to provide the basis for its allegations in a letter dated 9 September. GE Healthcare submitted this complaint, in which it essentially reiterated the baseless allegations from its 28 August letter. In doing so, not only did GE Healthcare fail to properly engage in inter-company dialogue as required under Paragraph 5.2 of the Constitution and Procedure, but it also added four new clauses of the Code that Bracco allegedly violated that were not specified in its 28 August letter. GE Healthcare also attempted to buttress its complaint with a misleading citation to a small and out-of-context piece of a very extensive record from a related litigation in the US.

By way of background, in December 2003 a Bracco-named entity filed a complaint against GE Healthcare in the US for false advertising. The decision in the case was still pending. Significantly, in that US litigation, the same allegations that GE Healthcare raised in this complaint were raised, and later dropped.

As explained below, contrary to GE Healthcare's allegations, the IMPACT study (Protocol IOP 107) was a prospective, randomised, double-blind, multicentre, parallel group study that followed all relevant clinical practice guidelines and resulted in a highly regarded, peer-reviewed journal article. The authors of the article and the investigators of the study were among the highest calibre and most prestigious researchers in the field. The prospective defining of patients, data and endpoints and the blinded combining of data from the VIRPACT and INVICTA studies to form IMPACT was entirely proper, and any failure to mention the protocol amendments combining the data in the IMPACT article or related promotional materials was completely irrelevant and would not affect readers' perception of the IMPACT data. As such, Bracco, did not believe the IMPACT article and related promotional materials were in breach of the Code.

VIRPACT and INVICTA were designed in early 2004 and began enrolment in November 2004. Both were prospective, randomised, double-blind, multicentre, parallel group studies sponsored by Bracco that compared the effects of iopamidol to iodixanol in patients with moderate-to-severe chronic kidney disease (serum creatinine stably equal or above 1.5mg/dL or a calculated creatinine clearance stably below 60ml/1.73 m^2). The only difference between the two studies was that VIRPACT patients were examined with liver computed tomography (CT) whereas INVICTA patients were examined by CT angiography of peripheral vessels.

VIRPACT and INVICTA studied, *inter alia*, CIN, which was an acute decline in renal function after administration of an iodinated contrast medium. The possible difference in renal tolerability between iodixanol, an iso-osmolar contrast medium (IOCM)

and low-osmolar contrast media (LOCM, like iopamidol and others), was much debated after the publication of the NEPHRIC study, which was sponsored by GE Healthcare, and a massive promotional campaign by GE Healthcare aimed at convincing doctors that iodixanol, the IOCM, caused a lower rate of CIN than LOCM. The NEPHRIC study only compared iodixanol to a single LOCM – iohexol – in 129 patients. In its promotional campaign, GE Healthcare tried to claim that the NEPHRIC study results could be extrapolated to all LOCM (including iopamidol), not just iohexol.

At the time of VIRPACT, INVICTA and IMPACT, chronic kidney disease was known to be the most important factor for the development of CIN. Therefore, all the patients in the VIRPACT and INVICTA studies were at high risk of CIN.

VIRPACT and INVICTA were run in parallel and several of the investigational sites were involved with both studies. Of note:

- all patients in both studies received the same intravenous dose (40g of iodine) of either iodixanol or iopamidol, at the same injection rate, independently of the CT examination to be performed;
- the inclusion/exclusion criteria of the two studies were the same (with the type of CT examination they had to receive being the only difference);
- the randomization and blinding procedures were the same;
- the safety controls were exactly the same in both studies, including the controls for CIN (ie measurement of serum creatinine at screening, baseline and at 48-72 [hours] following the administration of the contrast media);
- the central laboratories used in the two studies were the same, as well as the procedures and methods for collection of blood samples, sample storage, sample shipment, and laboratory analysis;
- the safety objectives and endpoints were the same in both studies.

By mid-2005, it became apparent that although enrolment for VIRPACT was relatively steady, enrolment for INVICTA was extremely slow and was predicted to become even slower. This was because physicians increasingly believed that MR angiography was a safer alternative to CT angiography due to the lower dose of contrast required and of the lower risk of complications derived from the contrast-enhanced MR procedure. In November 2005, the INVICTA investigators suggested stopping recruitment, since it was very difficult to find new patients (only 45 of an expected 120 patients had been enrolled). Conversely, recruitment was almost complete for VIRPACT (in the end, 121 patients were recruited).

Since the safety and CIN controls were identical in VIRPACT and INVICTA, and CIN was a very important and sensitive issue, external experts and investigators recommended combining the two studies and prospectively focusing on CIN (see the expert's statement). In considering those recommendations, it was concluded by all concerned that combining the data would, at the very least, be the most ethical decision, to avoid simply stopping INVICTA and wasting the corresponding data (and also the risks to patients from exposure to the trial agents) that had been collected thus far. A new protocol was prepared, Protocol 107 (the IMPACT study), with CIN as the primary objective. The same CIN endpoint in the VIRPACT and INVICTA studies, ie an absolute post-dose increase in serum creatinine equal or above 0.5mg/dL, was used for the new sample size estimate, which was prospectively made and based on the results of the NEPHRIC study.

Of note, everybody involved in the studies (patients, investigators, external experts, sponsor representatives) was still blinded to the contrast agents used in individual patients and to the overall rates of CIN. No interim analyses were performed. Enrolment in VIRPACT was completed at the end of November 2005, and enrolment in INVICTA was stopped in December 2005. The new protocol of IMPACT was designed in November 2005, reviewed by the investigators in December 2005 and signed off and submitted to the ethics committees/institutional review boards in January 2006. A new, prospectively defined statistical analysis plan was defined in January 2006. Data management was started in January 2006.

According to the new IMPACT protocol, prior to unblinding any of the study data, completing data management and performing statistical analyses, a Renal Safety Data Monitoring Board comprising three medical experts was established: Each member of this Board was a licensed physician and an expert in contrast media safety and CIN. One was also a nephrologist, highly experienced in CIN studies and statistical analyses.

This board was responsible for reviewing the renal safety data and other necessary related data (eg demographics, medical history, concomitant medication) of each patient in a blinded manner, and validating each patient to be included in the study's renal safety analyses. The board was also responsible for following validation of the patients to be included in the renal safety analyses, database lock, unblinding, and statistical analyses of the renal safety data and reviewing the renal safety results of the study. The three members of the board were also in charge of the preparation of the study manuscript dealing with the CIN results. The manuscript was later published in Investigative Radiology, a peer-reviewed journal with the second highest impact factor in radiology (according to surveys of the field).

The review by the board was performed in February

2006. At the end of that review, 13 patients (7.8% of the entire study population) were not considered eligible for the primary CIN analysis. Before the end of that review, nobody could know the denominator to use to calculate CIN rates and the data were still blinded. Data management and statistical analysis were outsourced to a contract research organization. Data management completed in February 2006; the blind was broken after the database of the study was locked; and the statistical analysis was performed and completed between the end of February 2006 and March 2006. The first, draft results were circulated to all the investigators in March 2006. The manuscript was submitted to Investigative Radiology in June 2006.

The IMPACT study results showed a lower rate of CIN following the LOCM iopamidol than was expected from GE Healthcare's extrapolation of the NEPHRIC study. In the NEPHRIC study, using the same CIN endpoint (an absolute increase in serum creatinine equal or above 0.5mg/dL from baseline), the rates of CIN had been 3% following the IOCM iodixanol and 26% following the LOCM iohexol. In the IMPACT study those rates were zero (no cases of CIN) following the LOCM iopamidol and 2.6% following the IOCM iodixanol.

In response to GE Healthcare's allegations in the US litigation, Bracco retrospectively examined the IMPACT database and checked how many cases of CIN were observed in the original VERPACT and INVICTA patients. No cases of CIN occurred in the INVICTA population. Of the 121 patients in VIRPACT, 112 were considered eligible for the CIN analysis by the Renal Safety Data Monitoring Board. The rates of CIN in VIRPACT were again zero for the LOCM iopamidol and 3.6% following the IOCM iodixanol ie higher than the rate of CIN for iodixanol in IMPACT. This evidence supported Bracco's contention that there was no ulterior motive to combine the studies, since combination did not enhance the iopamidol data (in fact quite the contrary, as the rate of CIN reported in patients receiving the IOCM iodixanol was 3.6% in the INVICTA study and 2.6% when combined in the IMPACT study).

Of note, in the manuscript, at the section 'Study Limitations', the following was reported:

> 'The sample size of the study was calculated based on the apparent differences between contrast agents in the NEPHRIC study. While the number of subjects reported here is higher than that in the NEPHRIC study (153 vs. 129), the incidence of CIN observed was lower than anticipated in planning this trial. However, the 95% confidence interval around the difference in incidence of a 0.5 mg/L increase in SCr seen between trial groups ranges from -6.2% to 1.0%. Thus, our results are compatible with an absolute difference in CIN rates of close to 6% in favour of iopamidol or 1% in favour of iodixanol. With the CIN incidence rates seen in the current trial, a study of about 3800 cases would be required to detect even a 50% reduction in the incidence of CIN with one contrast medium over the other.'

The incidence of CIN in VIRPACT and INVICTA were similar. Since: a) there were no cases of CIN following the LOCM iopamidol in either study; b) all (few) CIN cases were seen after iodixanol; and c) the power of VIRPACT or IMPACT alone would have been equally limited, the authors decided that it was irrelevant to mention the VIRPACT and INVICTA studies in any section of their manuscript (see the expert's statement).

In light of the above, GE Healthcare's allegations, ie that the studies 'were only combined after … statistical analysis [was] underway' and 'after a blinded analysis had been conducted', and that 'the decision to combine data was post-hoc subsequent to …commencement of statistical analysis' were completely false and had no support. The only support that GE Healthcare proffered for these statements were vague, highly selective statements that had been taken out of context, as set out in the expert's statement.

Contrary to the image that GE Healthcare attempted to paint, Bracco could have no improper commercial motive to avoid mentioning VIRPACT and INVICTA in its promotional materials. Indeed, if the studies had not been combined, as discussed above, Bracco could have possessed a study (VIRPACT) that showed even more remarkable trends of superiority of iopamidol over iodixanol.

Bracco did not believe that any of its promotional material breached any of the clauses of the Code. No reader would be misled by the absence of any reference to INVICTA and VIRPACT as IMPACT was a valid, reliable clinical study in its own right. Bracco was disappointed that GE Healthcare had chosen to repeat the allegation that the decision to combine the raw data from VIRPACT and INVICTA into the IMPACT study was only made '…after the overall CIN rates of these two studies could easily have been known'. Bracco made it crystal clear in the US litigation and repeated it here: the decision to combine the data might have led to Bracco forgoing an opportunity to claim a clinical superiority for its product over that of GE Healthcare. In the circumstances, the decision to combine the data was not a pre-meditated one based on commercial considerations.

For the reasons set forth above, Bracco requested that GE Healthcare's complaint be dismissed.

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The Director noted Bracco's submission regarding inter-company dialogue. GE Healthcare set out its initial concerns in a letter dated 28 August wherein it expressed concerns regarding the promotion of iopamidol using the IMPACT study stating that pertinent information about the conduct, design and analysis of the study had been omitted. Promotional materials did not accurately depict its conduct. The study methodology was of questionable validity.

Further GE Healthcare alleged that such actions, *inter alia*, brought discredit to the industry and referred to Clause 2. The Director did not consider that a complaint to the Authority had to use identical language to that used in inter-company correspondence. It was important, however, that a formal complaint was not inconsistent with inter-company dialogue. New matters could not be raised in the complaint. On that basis the Director considered that inter-company dialogue had taken place in relation to Clause 7.2, and the allegation that the promotional materials did not accurately depict the study methodology and thus lacked pertinent information, and Clause 2. The complaint on these points was referred to the Panel for consideration. The alleged breaches of Clauses 7.4, 7.10 and 9.1 had not been the subject of intercompany dialogue and thus were not considered by the Panel.

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PANEL RULING

The Panel noted that the published study, Barrett *et al* stated that it compared the effects on renal function of iopamidol-370 injection and iodixanol-320 in patients with chronic kidney disease undergoing contrast-enhanced multi-detector computed tomography examinations using a multi-centre, double-blind, randomised parallel group design. The study concluded that the rate of CIN in patients with moderate-to-severe chronic kidney disease was similarly low after intravenous administration of equi-iodine doses (40g) of iopamidol-370 or iodixanol-320 for contrast-enhanced multi-detector computed tomography. The materials and methods section discussed the study patients, protocol and statistical analysis. It appeared to be one study designed *de novo* to assess the primary outcome measure. The discussion section stated that the results of the trial failed to demonstrate any difference in the incidence of CIN between equi-iodine doses of iodixanol-320 and iopamidol-370 for IV use in patients with pre-existing stable chronically reduced kidney function. The study authors noted that this was at odds with the findings of a previous trial comparing a nonionic monomer, iohexol with iodixanol but consistent with findings in other prospective or retrospective studies. It was noted that several previous studies had weaknesses which detracted from the IMPACT study authors' ability to reach valid conclusions. The study authors then described IMPACT as the largest prospective, randomized, double-blind comparison of iodixanol with a non-ionic monomer. Study limitations were discussed including calculation of the sample size which was based on the apparent differences between contrast agents in the NEPHRIC study (Aspelin *et al*, 2003). Whilst the number of subjects in IMPACT was higher (153 vs 129) the incidence of CIN observed was lower than anticipated. The IMPACT study authors noted that with the CIN incidence rates in the trial a study of about 3,800 cases would be required to detect even a 50% reduction in the incidence of CIN with one contrast medium over the other.

The Panel noted Bracco's submission that the prospective defining of patients, data and endpoints was entirely proper and the failure to mention the protocol amendments combining the data in, *inter alia*, related promotional material was completely irrelevant and would not affect readers' perception of the IMPACT data. The Panel noted Bracco's submission about the respective methodologies applied in the INVICTA and VIRPACT studies. The safety objectives and endpoints were the same in both studies. Bracco had submitted a statement from an expert on the Renal Safety Data Monitoring Board established by the IMPACT protocol. The expert confirmed that the board undertook a blinded review of data from INVICTA and VIRPACT to make the required determinations including eligibility. CIN rates were not known until the blind was broken for statistical analysis when the data from the two studies was combined. The expert statement explained that the protocols were identical with respect to CIN and noted that there were no cases of CIN following iopamidol in either study; all of the very few cases of CIN occurred after iodixanol; and the power of VIRPACT or IMPACT alone would have been equally limited.

The Panel noted that GE Healthcare had provided a booklet entitled 'The Care Pathway Managing the Chronic Kidney Disease Patient in the Cardiology and Radiology Department'. A page headed 'Latest Clinical Evidence: The IMPACT Study' outlined the methodology from the published study and depicted the results in two bar charts. The first showed the percentage of patients with an increase in serum creatinine $\geq$ 0.5mg/dL from baseline (iopamidol-370, 0%, iodixanol-320, 2.6%; p=0.30). The second showed the percentage of patients with an increase in serum creatinine $\geq$25% from baseline (iopamidol-370, 3.9%, iodixanol, 4%; p=0.4). An asterisked statement beneath the bar charts read 'The observed differences in CIN rates were not statistically significant (p>0.05)'. The Panel was concerned that the first bar chart gave the immediate visual impression of a statistically significant difference between the products whereas the study failed to demonstrate a difference.

The Panel noted that promotional material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and queried whether the reader had been provided with sufficient information about the study methodology to enable them to decide how much weight to attach to the data.

The Panel noted that the secondary endpoint data from two separate studies had been combined to become the primary endpoint in the IMPACT study. The material gave the impression that the CIN data was originally derived from a study wherein it was a primary endpoint. That was not so. The position

was more complicated. The Panel also queried whether the study was sufficiently powered to detect a statistically significant difference. The Panel considered that on balance the failure to provide more information about the study methodology and sample size was a material omission and was misleading. A breach of Clause 7.2 was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

GE Healthcare had also provided a branded summary of the study (BUK010621). This reproduced the data shown in bar charts referred to above and on a key message page stated 'The results showed a low level of CIN, with no significant difference observed between the two contrast agents'. The Panel queried whether stating that there was no significant difference observed between the products fairly reflected the fact that the study failed to demonstrate a difference between the products bearing in mind the authors' comments about the low incidence of CIN and that given this a study of about 3,800 would be required to detect a 50% reduction in the incidence of CIN. The Panel considered that its comments above also applied to the study summary. The Panel considered that on the balance of probabilities the omission of pertinent information was misleading as alleged. A breach of Clause 7.2 was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

Complaint received **30 September 2008**

Case completed **19 December 2008**