**CASE AUTH/3103/10/18 ANONYMOUS, NON-CONTACTABLE v IPSEN**

**Promotion of Cabometyx**

**An anonymous, non-contactable complainant alleged that a meeting organised by Ipsen was a glorified sales pitch for Cabometyx (cabozantinib). Cabometyx was indicated for the treatment of advanced renal cell carcinoma (RCC).**

**The complainant stated that overall the meeting advocated the use of Cabometyx as the new gold standard. Side effects seemed only to occur with competitor products. Despite the mention of comparators, Votrient (pazopanib, marketed by Novartis) was not considered as a viable therapeutic option despite its effective use in first line therapy. Ipsen focused on Sutent (sunitinib, marketed by Pfizer) to publicise its new phase II study data irrespective of the current therapeutic landscape.**

**The complainant alleged that the meeting was biased and the scientific integrity of its content, questionable.**

**The detailed response from Ipsen is given below.**

**The Panel noted that materials associated with the meeting clearly stated that the meeting was promotional and was organised and funded by Ipsen; they included prescribing information for Cabometyx.**

**The Panel considered that the promotional nature of the meeting would be clear to those invited, Cabometyx was mentioned in the title of the meeting Stepping up: Bringing Cabometyx (cabozantinib) to the forefront of advanced renal cell carcinoma (RCC) treatment. The Panel did not consider that given the numerous mentions of the promotional nature of the meeting that those invited would have been expecting anything other than a promotional meeting. The Code required such meetings to include educational content. It was not disguised and the Panel therefore ruled no breach of the Code.**

**The Panel noted that according to the SPC the recommended dose of Cabometyx was 60mg once daily. Management of suspected adverse drug reactions might require temporary treatment interruption and/or dose reduction. When dose reduction was necessary it was recommended to reduce to 40mg daily and then to 20mg daily. Details for when dose interruptions were recommended were given.**

**The Panel noted Ipsen’s submission regarding the responses to an unprompted question from the Chair to the panel at the end of the real-world experience section in relation to whether they were starting all patients on 60mg cabozantinib.**

**The Panel noted that one speaker stated that he/ she would probably start at 60mg in normal weight patients but admitted that he/she needed to reduce to 40mg in a good number of patients which was then ‘very nicely tolerated’. Escalating the dose if a patient tolerated 40mg never happened, so it was better to reduce the dose.**

**The second speaker stated, however, that he/she often started patients on 40mg, particularly the older and smaller patients and would then work up and down from that. The speaker further stated that individualised decisions should be made but many patients were not on 60mg long term.**

**The Panel noted that the briefing material for company attendees was clear that questions concerning off-label use of the medicine would not be forwarded to the Chair. It stressed that promotional representatives could only discuss on licence and anything out of licence had to be referred to the medical department through the usual process. The Panel noted that the speakers and the Chair had been similarly briefed with regard to questions concerning off label use of the medicine.**

**The Panel noted that the Cabometyx SPC stated that no specific dose adjustment in older people (≥65 years) was recommended nor was there any mention of a dose adjustment recommendation based on weight. The Panel considered that Ipsen’s description of the second speaker’s comment with regard to older and smaller patients often starting on 40mg at Ipsen’s meeting amounted to advocating the use of a lower starting dose as alleged. This was inconsistent with the SPC and a breach of the Code was ruled. The Panel noted that Ipsen had briefed the speakers on the need to comply with the Code and that although the speaker was referring to his/her clinical approach, it was an established principle that pharmaceutical companies were responsible for what contracted speakers said on their behalf. Taking all the circumstances into account the Panel did not consider that the reference to starting older and smaller patients on 40mg meant that high standards had not been maintained and no breach of the Code was ruled. Further this did not bring discredit upon or reduce confidence in the pharmaceutical industry and the Panel ruled no breach of Clause 2.**

**The Panel noted that as submitted by Ipsen the presentation titled ‘The RCC treatment landscape: where are we now?’ included reference to pazopanib on a number of slides, and was variously referred to as first and second line therapy. The Panel did not consider that Votrient (pazopanib) was deliberately omitted or that it was not considered as a viable therapeutic option as alleged and the Panel therefore ruled no breach of the Code.**

**The Panel noted that the complainant had not provided any specific detail in relation to his/her concern that side effects seemed to only occur with competitor products. The Panel noted that the presentation titled ‘Cabometyx in advanced RCC’ referred to the adverse events experienced during Cabometyx registration studies. During the real world experience part of the meeting, adverse events with cabozantinib were described. In the Panel’s view the complainant had not provided evidence to show that Ipsen had misleadingly referred to only competitor medicines having side effects and not Cabometyx as alleged. No breach of the Code was ruled.**

**The Panel could find no reference to Cabometyx as the ‘new gold standard’ of care as alleged; it was described in the meeting closing remarks as a new first line option which helped set a new standard of care. The Panel further noted the complainant’s comment that the success of Ipsen advocating Cabometyx as the new gold standard was evident when a member of the audience asked if it would be used as a competitor in future clinical trials. According to Ipsen, the question asked was what impact the CABOSUN data would have on trials that were currently set up to have sunitinib as a current standard of care. The Panel considered that there was no evidence that Ipsen had advocated Cabometyx as the new gold standard as alleged and no breach of the Code was ruled.**

**The complainant was further concerned that Ipsen focused on sunitinib to publicise its new Phase II study irrespective of the current therapeutic landscape. The Panel noted Ipsen’s submission that in oncology generally, and in particular aRCC, the environment was rapidly evolving. This was a challenge for companies and clinicians because the pace of change often meant by the time a product became licensed, the comparator arm in the trial might no longer be a relevant standard of care. The Panel noted that CABOSUN was a Phase II study designed to evaluate the efficacy and safety of cabozanitinib vs sunitinib. In the Panel’s view it was not misleading for Ipsen to refer to sunitinib when discussing the CABOSUN study as it was the treatment in the comparator arm; Ipsen had within the meeting provided information on the current therapeutic landscape including currently licensed treatments and their position in the treatment guidelines referred to above. The Panel therefore ruled no breach of the Code.**

**The Panel noted that the meeting agenda referred to real-world experience with Cabometyx and not realworld evidence as referred to by the complainant. In the Panel’s view it was not necessarily unacceptable to refer to a selection of case studies to demonstrate real world experience provided the way in which it was done was not misleading and complied with the Code. The Panel did not consider that the complainant provided evidence to show that the three case studies were presented as real-world evidence as alleged. The case studies were clearly described as real-world experience and no breach of the Code was ruled.**

**The Panel noted its comments and rulings above and did not consider that Ipsen had failed to maintain high standards nor had it brought discredit upon or reduced confidence in the industry, no breach of the Code was ruled including no breach of Clause 2.**

An anonymous, non-contactable complainant complained about the promotion of cabozantinib by Ipsen Limited at a meeting in September 2018. Ipsen marketed cabozantinib as film-coated tablets (Cabometyx) for the treatment of advanced renal cell carcinoma.

**COMPLAINT**

The complainant stated that he/she had attended a meeting organised by Ipsen, in London with an option for virtual attendance from a centre or from home. The complainant stated that he/she was horrified and shocked to find that the meeting was just a glorified sales pitch for cabozantinib. Plenty of subliminal messages were eventually distilled into advocating the use of cabozantinib as the new gold standard. This proved to be effective as demonstrated by a question from a member of the audience querying whether cabozantinib would be used as a comparator in future clinical trials.

The complainant stated that while other companies endeavoured to follow the right route by providing evidence of safety and efficacy via the legitimate regulatory channels, Ipsen circumvented this and advocated the use of lower starting doses via the chairman, especially to those who had not used it before.

The section on real-world evidence comprised a handful of case studies. Notwithstanding that the definition of real-world evidence was unclear, it could not be based on the observation of a few patients to generalise and present as evidence. The in-built messages were a mixture of general comments woven in with facts intended to emphasise cabozantinib as the gold standard. Side-effects seemed to only occur with competitor products. Despite the individual mention of comparators, one was deliberately omitted. Votrient (pazopanib, marketed by Novartis) was not considered as a viable therapeutic option despite its effective use in first line therapy. Ipsen’s focus was on Sutent (sunitinib, marketed by Pfizer) to publicise its new phase II study data irrespective of the current therapeutic landscape.

The complainant alleged that the meeting content was highly biased, and the scientific integrity of its content questionable. Ipsen’s behaviour was unacceptable; it needed to step up.

When writing to Ipsen, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 7.4, 7.9, 9.1 and 12.1 of the Code.

**RESPONSE**

Ipsen explained that cabozantinib was a small molecule that inhibited multiple receptor tyrosine kinases. It was granted a marketing authorization in September 2016 for the treatment of advanced renal cell carcinoma (aRCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. In May 2018, the European Commission confirmed that cabozantinib had been granted a marketing authorization variation for the treatment of aRCC in treatment-naïve adults with intermediate or poor risk per the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria.

Ipsen assumed that the meeting to which the complainant referred, was one which it organised, funded and hosted on the evening of Wednesday, 26 September 2018. The title of the event was ‘Stepping Up: Bringing Cabometyx ▼(cabozantinib) to the forefront of advanced renal cell carcinoma (aRCC) treatment’. The title was aimed at representing the fact that the newer indication for the medicine, which received a marketing authorization this year, was for first line/front line patients. It was a promotional meeting focussed on educating appropriate UK health professionals involved in the clinical management of RCC on the use of Cabometyx for the treatment of aRCC. Ipsen submitted that the event had been meticulously and carefully planned and executed to meet the requirements of the Code and Ipsen’s high standards for the quality of content, and the company’s robust internal processes. The feedback received from the evening was very positive (copies of evaluation forms were provided).

Ipsen regretted that one of the attendees was horrified and shocked to find that the meeting was just a glorified sales pitch for Cabometyx. Working with a panel of leading international and UK experts in RCC management, the meeting was designed to provide fair, accurate, objective and balanced information regarding Cabometyx as a treatment option in aRCC to appropriate UK health professionals, in a manner compliant with the Code, in order to provide good quality medical education and thus help to improve patient care.

Ipsen noted that Clause 12.1 of the Code stated that promotional material and activities must not be disguised. Ipsen had acted in accordance with Clause 12.1, Clause 9.10 (‘Material relating to medicines and there uses, whether promotional or not, and information relating to human health or diseases which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company’) and Clause 22.4 (‘When meetings are sponsored by pharmaceutical companies, that fact must be disclosed in all of the papers relating to the meetings and in any published proceedings. The declaration of sponsorship must be sufficiently prominent to ensure that readers are aware of it at the outset’). The meeting was clearly advertised as a promotional event organised and funded by Ipsen. All invitations and other related documents and materials for the meeting (including its title) included a clear statement to that effect. Further, the content of the meeting, and the way in which it was presented and to whom, gave a very clear indication of its promotional nature which was aligned with Clause 1.2 (‘The term “promotion” means any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicines’). Ipsen provided copies of materials associated with the meeting, eg invitations and ‘Save the Date’ items.

Ipsen disputed the complainant’s submission that plenty of subliminal messages were eventually distilled into advocating the use of Cabometyx as the new gold standard for the following reasons:

1 The meeting was clearly advertised as a promotional meeting on the use of Cabometyx in aRCC, as outlined above, so attendees should have expected discussion on this treatment. Education was the primary purpose of this meeting and this was reflected in the objectives outlined in the meeting approval form, speaker briefings and in the relevant materials such as the programme and invitations.

2 The faculty comprised nationally and internationally recognised experts in the area with extensive experience across the treatment landscape for aRCC. Speaker biographies were provided in the meeting booklet (CMX-UK-001496).

3 The faculty was extensively briefed by Ipsen by way of a speaker contract, a written briefing, and a telephone/face-to-face briefing. The briefing document, contracts and a document containing extra briefing guidance were provided.

4 The presentations included full reference to all licensed products in the current treatment pathway, two sets of internationally recognised guidelines from reputable professional societies in oncology and a faculty-proposed treatment pathway consistent with both of the aforementioned;

5 All attendees had the opportunity to question the faculty. The questions were screened by the medical advisor (a qualified medical final signatory) before being passed on to the chair to ensure that they were not inconsistent with the particulars in the summary of product characteristics (SPC), nor likely to elicit answers inconsistent with the SPC.

6 Cabometyx was never labelled as a ‘gold standard’ during the meeting nor was there anything to suggest that the tyrosine kinase inhibitor (TKI) should be used as the treatment of choice. This was clearly supported by the accurate, fair, balanced, objective, unambiguous and up-to-date content of the presentations delivered during the meeting, consistent with Clause 7.2, and by the briefing delivered to the speakers before the meeting. Furthermore, the debate amongst the panel, and the summary in the penultimate slide from the meeting, focussed on whether Cabometyx should be considered as:

 a new standard of care in 1L aRCC patients of intermediate or poor risk. This was consistent with the SPC, current scientific opinion and international clinical guidelines.

 a standard of care in 2L patients previously treated with a vascular endothelial growth factor (VEGF)-targeted treatment. This was consistent with the SPC, current scientific opinion and international clinical guidelines.

7 Ipsen provided a full list of questions submitted by the attendees and in particular noted one question passed on to the chair which was ‘Could the faculty comment on how it feels about changing practice based on an underpowered phase 2 study? Are our regulatory bodies losing academic rigour?’. Ipsen submitted that the question demonstrated that it had facilitated a balanced debate about cabozantinib.

In summary, Ipsen did not agree with the complainant’s statement about advocating the use of Cabometyx as a gold standard for the reasons described above. Every effort was made to ensure that the information communicated to the audience was accurate, balanced and not misleading, particularly around the use of Cabometyx and its position within the treatment landscape. Ipsen referred to the speaker briefing document.

Ipsen noted that the complainant had referred to a question raised from a member of the audience querying whether Cabometyx would be used as a comparator in future clinical trials. Ipsen submitted that the question, ‘What do you think the impact of the CABOSUN data will have on trials that are currently set up to have sunitinib as a current standard of care?’, from a clinical research nurse who attended the meeting in London, was spontaneous and unprompted. This was a valid and appropriate question when new treatments became available. In oncology generally, and in aRCC in particular, the environment was rapidly evolving. This was a challenge for companies developing medicines and for clinicians involved in trials and the treatment of patients in routine clinical practice, because the pace of change often meant by the time a product became licensed, the comparator arm in the trial might no longer be a relevant standard of care eg the METEOR trial for Cabometyx. Although compared against everolimus (Afinitor, marketed by Novartis) as a standard of care when the trial began, it did not provide randomised controlled data compared to newer agents. Everolimus was now used in a limited number of patients in the second line setting in aRCC so it was therefore difficult for clinicians to make assessments of relative efficacy.

Ipsen stated that it did not advocate the use of lower starting doses as alleged.

The registration studies of Cabometyx (METEOR and CABOSUN) were presented in detail during the ‘Cabometyx in advanced RCC’ session and, the study designs, including the clinical trial starting dose of 60mg (consistent with the recommended dose in the SPC) were clearly displayed in the slides (CMX-UK-001658 Slides 18 and 38) and articulated verbally by the speaker.

Five slides, which appeared at the start of each presentation, stated where the Cabometyx prescribing information could be found; the prescribing information included the recommended starting dose of 60mg. The prescribing information also appeared at the end of every presentation. The case study presented by a speaker referred to a patient started on 60mg, which was documented on slide 7.

As stated above, Ipsen clearly briefed the speakers with a certified briefing, which included the statement: ‘All presentations must be consistent with the licensed indications of cabozantinib’ (ref CMX-UK-001500). In addition, prescribing information was sent to the speakers with the brief. Ipsen reinforced the briefing, and specifically mentioned the importance of referring to the licensed recommended dose on the briefing calls with the faculty.

The prescribing information was included in all applicable materials, both electronic and printed, distributed or displayed to health professionals as a part of this meeting, consistent with Clause 4.

During the panel discussion at the end of the realworld experience section, the chair asked the panel an unprompted and spontaneous question:

‘I just maybe want to ask something on dose, which is something we have not really, … talked a bit about it then we haven’t talked about it very much, with cabozantinib for people who are just starting to use the drug in the first place, are you starting everybody on 60mg? What’s your feeling? What feeling, we both use the drug I think quite a lot now, or is there a bit of variation on that, again in real world type of practice, again it is all about patients tolerating it, isn’t it?.’

In response to that question the panel members gave the following response:

‘So I would say in a normal weight patient I would probably start on 60mg but I have to admit that in a good number of patients we need to reduce to 40mg which is then very nicely tolerated. This was exactly what was also shown in the phase 3 trial METEOR trial, so probably if 60mg is quite challenging for many patients but 40mg is well tolerated. But we would nevertheless try to start on 60mg because then escalating the dose if a patient tolerates 40mg this never happens in fact, so better reducing the dose then also you can offer something because when a patient complains about side effects, you need to offer something, dose reduction is something you can offer, going from 40 escalating to 60 I think is difficult the other way around doesn’t really work in clinical practice.’

and

‘We often particularly with the older and smaller patients start at 40mg and then work up and down from that. Many of these patients, I only have second line experience very few of them are on the full dose of Sunitinib by the time we meet them and I think you need to be, you know you have to use individualised decisions but I would say many patients are not on 60 long term.’

Ipsen submitted that it had taken every opportunity to brief the speakers to ensure that they spoke in accordance with the terms of the marketing authorization and were not inconsistent with the particulars listed in the Cabometyx SPC. A video recording of the interaction noted above demonstrated that it was very brief, it was a statement purely of an individual clinician’s personal practice and experience and was, on the whole, not inconsistent with the SPC and the panel quickly moved the discussion on.

Given the information above, the use of a lower starting dose was not advocated by or on behalf of Ipsen during the meeting and every effort was made to ensure that the content of the presentations and the speakers’ briefs were not inconsistent with the Cabometyx SPC and in accordance with Clause 3.2 of the Code.

Ipsen submitted that the ‘real-world evidence section’ that the complainant appeared to refer to was the presentation on ‘Real-world experience with Cabometyx: The impact across the spectrum of aRCC’. The terms ‘real-word evidence’ and ‘realworld experience’ were not the same and thus were not to be used interchangeably. The segment of the meeting programme entitled ‘real-world experience’ was for the speakers to share their clinical experience gained in real-world practice. They were presented as case studies and were not presented in the context of real-world evidence. The presented cases were based on real patients, describing real events and the individual case studies were not presented in a way to suggest generalisability. The case studies were shared with the attendees who were all specialists in oncology and RCC and therefore it was appropriate and was fully understood in the context it was presented.

During this presentation, three patient cases were presented by two speakers. The purpose was to demonstrate the clinicians’ real-life experience of managing aRCC patients in the second line setting in their clinical practice and not to generalise the case study findings.

With regard to the complainant’s comment that ‘side-effects seemed to only occur with competitor products’, Ipsen noted that the case studies presented on Cabometyx included a number of adverse drug reactions related to its use, and therefore upheld the principle of Clause 7.9.

Case study 1 included an adverse drug reaction of hypomagnesaemia experienced as a result of treatment with Cabometyx. In the same case study, the patient had a 9-month response to treatment with Cabometyx, and on progression started treatment with nivolumab (Opdivo, marketed by Bristol-Myers Squibb), to which the patient had no documented adverse reactions and a good response and he/she currently remained on that treatment.

The case study presented by a speaker included adverse reactions for a patient who received Cabometyx as a second line treatment including diarrhoea grade 3 when receiving a 60mg dose and following dose reduction to 40mg experienced grade 2 hypertension, diarrhoea and hand-foot syndrome and grade 1 hypothyroidism, fatigue, dysphonia and hair and skin-depigmentation (slides 7 and 8, CMX-UK-001676).

In summary, the case studies presented during the meeting were not atypical of individual patients in clinical practice. Every effort was made to ensure the results were not misconstrued as ‘real-world evidence’ and that they did not mislead on the efficacy and tolerability of Cabometyx.

With regard to the allegation that pazopanib had been deliberately omitted, Ipsen noted that the presentation entitled: ‘The RCC treatment landscape: where are we now?’ included a balanced representation of the currently licensed treatments for aRCC. Slide 7 featured a timeline which outlined the year of marketing authorization granted for all licensed products in aRCC since 2006, not just Cabometyx. Pazopanib was documented on that slide. Slides 8 and 9 showed the current treatment guidelines for metastatic clear cell RCC from the European Association of Urology (EAU) and the European Society of Medical Oncology (ESMO), which had been adapted for currently licensed treatments. Pazopanib was referred to on slide 8 as a first-line treatment in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favourable-risk disease patients and on slide 9 as first- and second-line standard treatment choices for clear cell RCC and as a therapeutic option for nonclear cell RCC.

On slide 16, a treatment pathway proposed by an internationally-recognised expert in aRCC, consistent with current scientific opinion (as evidenced by the aforementioned guidelines) included pazopanib as a first-line treatment option for metastatic clear-cell RCC.

In summary, Ipsen stated that the complainant’s statement about pazopanib was incorrect. Pazopanib had been mentioned on numerous slides within the appropriate presentation and was considered a treatment option for aRCC.

Ipsen stated that the presentation entitled ‘Cabometyx in advanced RCC’ (ref CMX-UK-001657) included a balanced representation of the two registration trials for Cabometyx – CABOSUN and METEOR. Ipsen noted the complainant’s comment regarding Ipsen’s ‘focus on sunitinib’. Cabometyx was licensed for untreated patients with aRCC of intermediate or poor risk as defined by IMDC criteria as a result of CABOSUN trial where cabozantinib was compared to sunitinib. It was therefore only appropriate to focus on sunitinib as a comparator because it was consistent with the data in the summary of product characteristics (SPC), and crosstrial comparison would be inappropriate. Ipsen’s view was that any attempt to compare cabozantinib to pazopanib would not be consistent with Clause 7 of the Code.

In summary, Ipsen stated that the meeting fully represented the available treatment options and the current treatment pathway consistent with published data from the phase 2 CABOSUN trial, and current scientific opinion.

**General comments relating to Clause 7**

Ipsen noted that the meeting was a single event comprised of the following presentations:

Chair’s welcome and introduction to the UK environment for advanced RCC management, Cabometyx in advanced RCC; The RCC treatment landscape: where are we now?; Cabometyx in advanced RCC; Real world experience with Cabometyx: the impact across the spectrum of advanced RCC and summary and hub meeting close.

The overall balance of the presentations reflected the efficacy and safety balance for Cabometyx as a treatment for advanced renal cell carcinoma, and all presentations were substantiated. As part of the presentations, the full study design, primary endpoint, relevant secondary endpoints, and summary of safety information were presented by one member of the faculty. This could be found on slides 16-20, 26, 35, 38-45 of the Cabometyx in aRCC presentation. The safety and efficacy of the TKI was also highlighted by the speakers for the individual patient cases during the session: ‘Realworld experience with Cabometyx: The impact across the spectrum of advanced RCC’, which demonstrated actual patient adverse drug reactions seen by clinicians in the clinical setting. Slides 3 and 7 of the chair’s introduction included an overview of the objectives of the meeting and one slide outlined the licensed indications for all currently approved treatments for aRCC.

In summary, Ipsen stated that it had demonstrated that none of the presentations were inconsistent with the marketing authorization for Cabometyx and they all met the requirements of the Code. The information presented on the efficacy and safety of the product was accurate and balanced.

Ipsen stated that patients with aRCC, and in particular with intermediate or poor risk RCC per IMDC criteria, by definition had a very poor prognosis and it was an area of unmet clinical need. Ipsen was proud of the work it did to help improve the outcomes of patients with aRCC, and took seriously its responsibility to ensure promotional activities were carried out in a manner that was not inconsistent with the marketing authorization of Cabometyx, which protected and promoted patient safety, provided valuable medical education to relevant health professionals so as to improve patient care, and upheld the reputation of the UK pharmaceutical industry.

**PANEL RULING**

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that anonymous complaints would be accepted but that like all other complaints, the complainant had the burden of proving his/ her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties.

The Panel noted that the save the date printed and electronic notifications, template for emailing the save the date information, invitations, and meeting agenda clearly stated that the meeting was promotional and was organised and funded by Ipsen. The documents included prescribing information for Cabometyx. The Ipsen key account managers were to discuss the meeting in more detail when showing the invitation to the health professional. The registration confirmation and reminder sent by Cabometyx marketing, stated that the meeting was promotional and included prescribing information. The registration portal pages also mentioned that the meeting was promotional on the registration page and included access to the prescribing information and the SPC. The rolling banner, meeting booklet, webcast pages and signing in sheets stated that the meeting was promotional. The speakers’ slides stated that the meeting was a promotional meeting.

The Panel considered that it would be clear to those invited to the meeting, whether that be to the London venue or other venues or online, that the meeting was promotional. Health professionals would be very aware that the meeting was organised by Ipsen about one of its products; Cabometyx was mentioned in the title of the meeting (Stepping up: Bringing Cabometyx (cabozantinib) to the forefront of advanced renal cell carcinoma (RCC) treatment) which was included on the materials listed above. The Panel did not consider that given the numerous mentions of the promotional nature of the meeting that those invited would have been expecting anything other than a promotional meeting. The Code required such meetings to include educational content. It was not disguised and the Panel therefore ruled no breach of Clause 12.1.

The Panel noted that the Ipsen briefing documents for speakers and chairs were clear regarding the need to comply with the ABPI Code and that questions about unlicensed medicines or indications could not be answered during the event. Ipsen’s medical information department would respond to such questions.

The Panel noted that according to the SPC the recommended dose of Cabometyx was 60mg once daily. Treatment should continue until the patient was no longer clinically benefitting from therapy or until unacceptable toxicity occurred. Management of suspected adverse drug reactions might require temporary treatment interruption and/or dose reduction. When dose reduction was necessary it was recommended to reduce to 40mg daily and then to 20mg daily. Details for when dose interruptions were recommended were given. Dose reductions were recommended for events that if persistent could become serious or intolerable. Section 4.4 Special warnings and precautions for use of the SPC referred to most events occurring early in the course of treatment and the need for the physician to evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications were warranted. The SPC referred to renal cell carcinoma following prior VEGF targeted therapy and that dose reductions and dose interruptions due to adverse events occurred in 59.8% and 70% respectively of cabozantinib treated patients in the pivotal clinical trial (METEOR). Two dose reductions were required in 19.3% of patients. The median time to the first dose reduction was 55 days and to the first dose interruption was 38 days. In treatment-naïve renal cell carcinoma, dose reductions and dose interruptions occurred in 46% and 73%, respectively, of cabozantinib treated patients in the clinical trial (CABOSUN).

The Panel noted Ipsen’s submission regarding the responses to an unprompted question from the Chair to the panel at the end of the real-world experience section in relation to whether they were starting all patients on 60mg cabozantinib.

The Panel noted that one speaker stated that he/ she would probably start at 60mg in normal weight patients but admitted that he/she needed to reduce to 40mg in a good number of patients which was then ‘very nicely tolerated’ and this was what was also shown in the METEOR trial. He/she would nevertheless try to start patients on 60mg because escalating the dose if a patient tolerated 40mg never happened, so it was better to reduce the dose. Dose reduction could then be offered if a patient complained about side effects.

Another speaker stated, however, that he/she often started patients on 40mg, particularly the older and smaller patients and would then work up and down from that. The speaker further stated that individualised decisions should be made but many patients were not on 60mg long term.

The Panel noted that the briefing material for company attendees was clear that questions concerning off label use of the medicine would not be forwarded to the Chair. It stressed that promotional representatives could only discuss on licence and anything out of licence had to be referred to the medical department through the usual process. The Panel noted that the speakers and the Chair had been similarly briefed with regard to questions concerning off label use of the medicine.

The Panel noted that the Cabometyx SPC stated that no specific dose adjustment in older people (≥65 years) was recommended nor was there any mention of a dose adjustment recommendation based on weight. The Panel considered that Ipsen’s description of the second speaker’s comment with regard to older and smaller patients often starting on 40mg at Ipsen’s meeting amounted to advocating the use of a lower starting dose as alleged. This was inconsistent with the SPC and a breach of Clause 3.2 of the Code was ruled. The data in the SPC showed that many patients had dose reductions. The Panel noted the company’s instructions regarding the need to comply with the Code and that the speaker was referring to his clinical approach. The Panel noted, however, that it was an established principle that in such circumstances, pharmaceutical companies were responsible for what contracted speakers said on their behalf. Taking all the circumstances into account the Panel did not consider that the reference to starting older and smaller patients on 40mg meant that high standards had not been maintained and no breach of Clause 9.1 was ruled. Further this did not bring discredit upon or reduce confidence in the pharmaceutical industry and the Panel ruled no breach of Clause 2 of the Code.

The Panel noted that as submitted by Ipsen the presentation titled ‘The RCC treatment landscape: where are we now?’ included reference to pazopanib on a number of slides. Slide 7 featured a timeline which outlined the year of marketing authorization granted for RCC products in Europe since 2006. Slides 8 and 9 showed the current treatment guidelines for metastatic clear cell RCC from the European Association of Urology (EAU) and the European Society of Medical Oncology (ESMO), which had been adapted for currently licensed treatments. Pazopanib was referred to on slide 8 as a first-line treatment in IMDC favourablerisk disease and IMDC intermediate and poor-risk disease patients and on slide 9 as first-and secondline standard treatment choices for clear cell RCC and as a therapeutic option for non-clear cell RCC. According to Ipsen, slide16 showed a treatment pathway proposed by an internationally-recognised expert in RCC, consistent with current scientific opinion (as evidenced by the aforementioned guidelines) included pazopanib as a first-line treatment option for metastatic clear-cell RCC. Pazopanib was further mentioned in the presentation titled ‘Cabometyx in advanced RCC’. The Panel did not consider that Votrient (pazopanib, marketed by Novartis) was deliberately omitted or that it was not considered as a viable therapeutic option as alleged and the Panel therefore ruled no breach of Clause 7.2.

The Panel noted that the complainant had not provided any specific detail in relation to his/her concern that side-effects seemed to only occur with competitor products. The Panel noted that the presentation titled ‘Cabometyx in advanced RCC’ which discussed the two main Cabometyx registration studies referred to the adverse events experienced during those studies. Further, the conclusion slide of that presentation stated, inter alia, that the side effect profile of Cabometyx was well known and not really different from tyrosine kinase inhibitos (TKIs) that had been used over the last 12 years and advised that proactive adverse event management was crucial.

The Panel further noted that whilst the presentation of the first case study during the real-world experience section stated that cabozantinib was generally well tolerated, it stated that the patient experienced hypomagnesaemia as a result of treatment with Cabometyx. In the same case study, the patient had a 9-month response to treatment with cabozantinib and on progression started treatment with nivolumab (Opdivo, marketed by Bristol-Myers Squibb), which the patient appeared to have tolerated well with a good response. The second case study involved a patient who was changed from sunitinib to cabozantinib due to significant skin toxicity experienced whilst on sunitinib and appeared to have minimal side effects whilst on cabozantinib. The third case study involved a patient that had to have a dose reduction from 60mg to 40mg cabozantinib after three weeks due to a prolonged episode of Grade 3 diarrhoea. A number of adverse events were listed that were experienced after the dose reduction including Grade 2 hypertension, diarrhoea and hand-foot syndrome and Grade 1 hypothyroidism, fatigue, dysphonia, and hair and skin depigmentation. In the Panel’s view the complainant had not provided evidence to show that Ipsen had misleadingly referred to only competitor medicines having side effects and not Cabometyx as alleged and no breach of Clauses 7.2 and 7.9 were ruled.

The Panel could not find reference in the presentations to Cabometyx as the ‘new gold standard’ of care as alleged; it was described in the meeting closing remarks as a new first line option which helped set a new standard of care for treatment of aRCC patients which in the Panel’s view reflected the marketing authorization variation that was granted for the treatment of aRCC in treatmentnaïve adults with intermediate or poor risk. The Panel further noted the complainant’s comment that the success of Ipsen advocating Cabometyx as the new gold standard was evident when a member of the audience asked if it would be used as a competitor in future clinical trials. The Panel noted that the presentations included reference to licensed products in the current treatment pathway and two sets of internationally recognised guidelines from professional societies in oncology. The Panel noted Ipsen’s submission that a faculty-proposed treatment pathway consistent with both of the aforementioned guidelines was also included. Further, according to Ipsen, the question asked by the audience member was what impact the CABOSUN data would have on trials that were currently set up to have sunitinib as a current standard of care. The Panel considered that there was no evidence that Ipsen had advocated Cabometyx as the new gold standard as alleged and no breach of Clauses 7.2 and 7.4 were ruled. The complainant was further concerned that Ipsen focused on sunitinib to publicise its new Phase II study irrespective of the current therapeutic landscape. The Panel noted Ipsen’s submission that in oncology generally, and in particular aRCC, the environment was rapidly evolving. This was a challenge for companies developing medicines and for clinicians involved in trials and the treatment of patients in routine clinical practice, because the pace of change often meant by the time a product became licensed, the comparator arm in the trial might no longer be a relevant standard of care. The Panel noted that CABOSUN was a Phase II study designed to evaluate the efficacy and safety of cabozanitinib vs sunitinib in patients with previously untreated locally advanced or metastatic RCC. In the Panel’s view it was not misleading for Ipsen to refer to sunitinib when discussing the CABOSUN study as it was the treatment in the comparator arm; Ipsen had within the meeting provided information on the current therapeutic landscape including currently licensed treatments and their position in the treatment guidelines referred to above. The Panel therefore ruled no breach of Clause 7.2.

The Panel noted that the meeting agenda referred to real world experience with Cabometyx and not real world evidence as referred to by the complainant. In the Panel’s view it was not necessarily unacceptable to refer to a selection of case studies to demonstrate real world experience provided the way in which it was done was not misleading and complied with the Code. The Panel did not consider that the complainant provided evidence to show that the three case studies were presented as real world evidence as alleged. In the Panel’s view the case studies were clearly described as real-world experience, and thus the Panel ruled no breach of Clauses 7.2 and 7.4.

The Panel noted its comments and rulings above and did not consider that Ipsen had failed to maintain high standards nor had it brought discredit upon or reduced confidence in the industry and no breach of Clauses 9.1 and 2 were ruled.

**Complaint received 3 October 2018**

**Case completed 6 December 2018**