CASES AUTH/2506/5/12 and AUTH/2507/5/12

ASTRAZENECA v LILLY and DAIICHI-SANKYO

Efient Leavepiece

AstraZeneca complained about an Efient (prasugrel) leavepiece issued by Lilly and Daiichi-Sankyo.

Efient, co-administered with acetylsalicylic acid (ASA), was indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) or ST segment elevation myocardial infarction (STEMI) undergoing primary or delayed percutaneous coronary intervention (PCI). Section 4.2 of the Efient summary of product characteristics (SPC), Posology and method of administration, stated that in patients with ACS who were managed with PCI, 'premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless discontinuation of Efient is clinically indicated'.

AstraZeneca stated that the leavepiece focussed on the STEMI subgroup of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thromobosis in Myocardial Infarction) study (pivotal registration study for Efient).

TRITON-TIMI 38 (Wiviott *et al*, 2001) was a Phase 3 trial involving patients with moderate to high risk ACS with scheduled PCI and compared Efient with clopidogrel. All patients received ASA. The primary efficacy endpoint was death from cardiovascular causes, non fatal myocardial infarction (MI) or non fatal stroke. The key safety endpoint was major bleeding.

AstraZeneca alleged that the leavepiece was inaccurate, misleading, played down major bleeding/safety considerations, promoted the off-label use of Efient beyond its maximum licensed duration of treatment, and as a result brought the industry into disrepute.

The detailed comments from Lilly and Daiichi-Sankyo are given below.

Page 1 of the leavepiece had across its top, 'Efient Proven Protection for ACS-PCI Patients Receiving Aspirin – Recommended for up to 12 Months'. Beneath, a prominent green band with larger white type bore the claim 'How can you make a difference for your ACS-PCI Patients?' followed by two sub headings 'STEMI Patients' and 'Help Give Your High Risk ACS-PCI Patients Superior Protection Against CV [cardiovascular] Events By Choosing Efient vs Clopidogrel'.

A graph headed 'TRITON-TMI [*sic*] 38, pre-specified STEMI subgroup analysis of the primary efficacy endpoint* and key safety endpoint at 15 months (n=3,534)' was referenced as adapted from Montalescot *et al* (2009). The explanation for * in the graph title was given towards the bottom of page 1 as 'Efient significantly reduced the composite endpoint of CV death, non-fatal MI or non-fatal stroke vs. clopidogrel' and ** as 'No significant difference in incidence of non-CABG [coronary artery bypass graft surgery] related TIMI major bleedings vs. clopidogrel'.**

The graph compared patients treated with clopidogrel + ASA and Efient + ASA in relation to CV death, MI, stroke and days from randomization. Non-CABG TIMI major bleeds were also compared for the two groups. The graph included data from 0 – 450 days from randomization and a vertical dotted line labelled 'Recommended length of treatment' indicated what appeared to be 365 days. On the right hand side of the graph was a prominent downward arrow labelled '21% RRR' [relative risk reduction]. Beneath this the actual risk reduction (ARR) was given in much smaller type 'ARR = 2.4%' p=0.0221' in favour of Efient in relation to CV death, MI, stroke. The comparison of non-CABG TIMI major bleeds did not show a statistically significant difference (p=0.6451).

AstraZeneca alleged that the title of the graph referred to analysis of the primary efficacy endpoint and key safety endpoint at 15 months yet the Efient SPC stated that it was recommended for use in adult patients up to 12 months only. This therefore promoted Efient beyond the terms of its licence and was misleading.

Further the graph illustrated a subgroup analysis of the primary endpoint, including RRR and ARR figures based on outcomes at 15 months. A faint dotted line was presented at 12 months showing the recommended (and therefore licensed) maximum duration of treatment, however the graph continued far beyond this point. The off-licence promotion was compounded by there being no presentation of the actual data, for example ARR and RRR figures, at 12 months. This created the impression that Efient could and should be used in excess of the maximum licensed duration of treatment.

AstraZeneca also alleged that the information was presented as showing no significant difference between Efient and clopidogrel in relation to non-CABG-TIMI major bleeds. While this might be the case in this specific subgroup, in the overall TRITON-TIMI 38 study Efient demonstrated significantly higher rates of non-CABG TIMI major bleeding (2.4% vs 1.8%, p=0.03), life threatening bleeding (1.4% vs 0.9%, p=0.01) and fatal bleeding (0.4% vs 0.1%, p=0.002). There was no mention of the overall results to provide context for clinicians to make an informed decision in relation to these serious

outcomes. AstraZeneca alleged that this was therefore inaccurate, misleading and did not reflect high standards.

The Panel noted that Section 4.2 of the Efient SPC, Posology and method of administration, stated that 'A treatment of up to 12 months is recommended, unless the discontinuation of Efient is clinically indicated …'. The graph at issue on page one of the leavepiece included a dotted line labelled 'Recommended length of treatment' at what appeared to be 365 days from randomization. The calculations for RRR and ARR appeared to be at the end of the study, ie 15 months.

The Panel noted that Section 4.8 (Undesirable effects) and 5.1 (Pharmacodynamic properties) of the Efient SPC referred to data at 14.5 months.

The Panel noted that the 15 month data was taken from the TRITON-TIMI 38 study, a pivitol registration study for Efient. Study visits were conducted at hospital discharge, at 30 days, 90 days and 3 months intervals thereafter for a total of 6 to 15 months. The prespecified subgroup analysis on patients with STEMI included detailed results for major efficacy and safety endpoints at 30 days and 15 months. The primary endpoint was CV death, non-fatal myocardial infarction or non-fatal stroke. The subgroup analysis had not been carried out at 12 months.

The Panel considered that the 15 month data would be of interest to prescribers. The SPC clearly referred to data beyond 12 months. The Panel considered that whilst it was acceptable to refer to the SPC data such references should be secondary to the statement at Section 4.2 of the SPC that treatment of up to 12 months was recommended.

The Panel noted that although the dotted line on the graph did not state the actual length of treatment, it could be approximately determined from the x axis. Neither the dotted line on the graph, nor the strapline at the top of the page which included the phrase 'Recommended for 12 months' were visually prominent. The Panel did not consider that the material on the page in question could be qualified by references to 12 month data in subsequent pages or in the prescribing information. The heading referred to a pre-specified STEMI subgroup analysis of the primary efficacy endpoint and key safety endpoint at 15 months appeared in a highlighted green box and was visually prominent. It made no mention of the recommended duration of treatment. The graph beneath depicted and analysed data at 450 days. The Panel considered that the heading was misleading about the recommended treatment period and consequently inconsistent with the SPC. Breaches of the Code were ruled.

The Panel noted that the graph made claims in relation to primary efficacy outcomes at 15 months. Other than the lines on the graph there was no mention or presentation of the actual ARR, or any other data, at 12 months.

The Panel noted that whilst a dotted line on the graph represented the recommended treatment period by presenting the efficacy and safety results at 15 months prominently with no data at 12 months the graph in effect promoted Efient for 15 months treatment. The 15 month data was not secondary to and or placed within the context of the 12 month recommended treatment period. This was misleading and inconsistent with the SPC recommendation. Breaches of the Code were ruled.

In relation to the results for non-CABG TIMI major bleeds the Panel noted that the subgroup analysis showed no significant difference between clopidogrel + ASA and Efient + ASA. The overall outcome in this regard in TRITON-TIMI 38 was statistically significant in favour of clopidogrel + ASA for the key safety endpoint. Further, the data for life threatening bleeding and fatal bleeding were also in favour of clopidogrel + ASA.

The Panel considered that the allegation that the graph demonstrated a subgroup analysis of non-CAGB TIMI major bleeds at 15 months contrary to the maximum licensed duration of treatment of 12 months was covered by its ruling of a breach set out above.

The overall safety results had not been included and the Panel considered that the subgroup analyses had not been placed in context. The balance of the evidence had not been presented. Breaches were ruled. As the data related to safety endpoints high standards had not been maintained and a further breach was ruled.

Page 2 of the leavepiece was headed 'Make A Difference Now to Protect Their Future'. A bar chart followed by a graph were presented on this page. The main heading to the bar chart was 'Confidence To Reduce The Risk Of Stent Thrombosis vs. Clopidogrel'. The bar chart was headed 'TRITON-TIMI 38: pre-specified STEMI subgroup analysis of the secondary efficacy endpoint of stent thrombosis at 15 months (n=3,534)'. The bar chart was adapted from Montalescot *et al* and compared the incidence of definite or probable stent thrombosis of Efient + ASA and clopidogrel + ASA. A prominent downward arrow labelled '42% RRR' appeared above the Efient bar. The ARR of 1.2%, p=0.0232 was given in less prominent smaller font on the left hand side of the bar chart. The claim 'Efient significantly reduced the risk of stent thrombosis compared with clopidogrel' appeared alongside the heading on the left hand side of the bar chart.

The second half of the page was headed 'Confidence to Reduce Recurrent Cardiovascular Events vs. Clopidogrel' beneath which was the heading 'TRITON-TIMI 38: Landmark analysis of time from first event to second event by randomised therapy (n=1,203)'. The graph below showed data adapted from Murphy *et al* (2008) which compared primary endpoint events (CV death, non-fatal MI or non-fatal stroke) for Efient + ASA and clopidogrel + ASA for 450 days from first event to second event or last follow-up. A dotted line was given on the graph to show recommended length of treatment. The results at 450 days were given. A prominent downward arrow labelled '35% RRR' appeared adjacent to the graph above the smaller much less

prominent figure 'ARR = 4.6% (p=0.016)'. The claim 'Among patients with an initial non-fatal cardiovascular event, Efient significantly reduced second events compared with clopidogrel' appeared alongside the graph.

AstraZeneca stated that the title and body of the bar chart referred to analysis of the secondary efficacy endpoint at 15 months yet Efient was recommended for use in adult patients up to a maximum of 12 months only. AstraZeneca alleged promotion beyond the licence, which was misleading.

With regard to the graph illustrating the endpoint of secondary CV events in the STEMI subgroup, AstraZeneca alleged that as the SPC recommended Efient for use in adult patients up to a maximum of 12 months only, the graph promoted beyond the licence and was misleading.

The Panel noted its general comments above about the recommended treatment period. The Panel further noted that there was no prominent mention on page 2 that treatment up to 12 months was recommended.

The Panel considered that the bar chart and its heading which referred to analysis at 15 months were inconsistent with the SPC and misleading. Breaches of the Code were ruled.

The Panel noted that Murphy *et al* looked at the recurrence of the primary endpoint events in TRITON-TIMI 38 with Efient compared with clopidogrel and concluded that Efient reduced both first and subsequent cardiovascular events at 15 months compared with clopidogrel in patients with ACS.

The Panel noted that the RRR claim for the advantage for Efient + ASA compared to clopidogrel + ASA was based on 15 month data. The Panel noted that the graph featured a dotted line at 12 months which represented the recommended treatment period. However by presenting the results at 15 months prominently the graph promoted the use of Efient for 15 months. This was misleading and inconsistent with the SPC recommendation. Breaches of the Code were ruled.

AstraZeneca noted that page 3 was headed 'Compared with Clopidogrel, Efient Offers:

- **Consistent platelet inhibition in healthy subjects**
- **Superior, long-lasting CV protection for 12 months of therapy**
- **No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients'.**

The final bullet point again did not mention or reference the fact that in TRITON-TIMI 38 study, there were significantly worse bleeding rates seen with Efient vs clopidogrel. AstraZeneca alleged that this was not a balanced reflection of all available data, was misleading and did not reflect high standards.

In summary, AstraZeneca alleged that the leavepiece contained multiple misleading claims relating to efficacy and safety; promoted the off licence use of Efient; did not maintain high standards and did not accurately convey the incidence of serious side-effects seen with Efient by clearly providing the contradictory results of the TRITON-TIMI 38 study. Given the repeated nature and totality of these issues, and particularly with respect to the last and most serious point, AstraZeneca alleged a reduction in confidence in the industry as a whole in breach of Clause 2.

The Panel noted its previous comments about the differences in outcomes between safety data in Montalescot *et al* and TRITION-TIMI in point 1 above. Whilst the claim 'No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients' was an outcome of the subgroup analyses it did not reflect the authors caveats nor was it placed in the context of the outcomes of the TRITON-TIMI study as a whole. This was not a fair reflection of the data. High standards had not been maintained in breach of the Code. Breaches of the Code were ruled.

With regard to the alleged breach of Clause 2 in relation to the leavepiece as a whole the Panel noted that Clause 2 was used as a particular sign of censure and reserved for such use. The Panel considered that given its rulings, particularly those in relation to the presentation of safety data above, the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

AstraZeneca UK Limited submitted a complaint about a four page Efient (prasugrel) leavepiece (ref UKEFF00714a) issued by Eli Lilly and Company Limited and Daiichi-Sankyo UK Limited. The leavepiece was headed 'How can you make a difference for your ACS-PCI Patients?'.

Efient, co-administered with acetylsalicylic acid (ASA), was indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) or ST segment elevation myocardial infarction (STEMI) undergoing primary or delayed percutaneous coronary intervention (PCI). Section 4.2 of the Efient summary of product characteristics (SPC), Posology and method of administration, stated that in patients with ACS who were managed with PCI, 'premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless discontinuation of Efient is clinically indicated'.

The leavepiece in question was withdrawn on in May 2012 in order for changes to be made. AstraZeneca maintained that the withdrawal of the leavepiece was not due to successful inter-company dialogue. Daiichi-Sankyo and Lilly stated that various inter-company discussions about AstraZeneca's concerns were unsuccessful.

AstraZeneca alleged that the material was in breach of several clauses of the Code as it was inaccurate, misleading, played down major bleeding/safety considerations, promoted the off-label use of Efient beyond its maximum licensed duration of treatment, and as a result brought the industry into disrepute.

AstraZeneca stated that the leavepiece focussed on the STEMI subgroup of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombosis in Myocardial Infarction) study (pivotal registration study for Efient). AstraZeneca stated that the approach seen in the leavepiece was used extensively throughout promotional materials for Efient.

TRITON-TIMI 38 (Wiviott *et al*, 2001) was a Phase 3 trial involving patients with moderate to high risk ACS with scheduled PCI and compared Efient with clopidogrel (Plavix, a Sanofi product). All patients received ASA. The primary efficacy endpoint was death from cardiovascular causes, non fatal myocardial infarction (MI) or non fatal stroke. The key safety endpoint was major bleeding.

1 **Graph headed 'TRITON-TMI [*sic*] 38: pre-specified STEMI subgroup analysis of the primary efficacy endpoint* and key safety endpoint** at 15 months (n = 3,534)'.**

This appeared on page 1 of the leavepiece.

Page 1 had an orange band across the top on which was written in white type, 'Efient Proven Protection for ACS-PCI Patients Receiving Aspirin – Recommended for up to 12 Months'. Beneath, a prominent green band with larger white type bore the claim 'How can you make a difference for your ACS-PCI Patients?' followed by two sub headings 'STEMI Patients' and 'Help Give Your High Risk ACS-PCI Patients Superior Protection Against CV [cardiovascular] Events By Choosing Efient vs Clopidogrel'.

The graph was referenced as adapted from Montalescot *et al* (2009). The explanation for * in the graph title was given towards the bottom of page 1 as 'Efient significantly reduced the composite endpoint of CV death, non-fatal MI or non-fatal stroke vs. clopidogrel' and ** as 'No significant difference in incidence of non-CABG [coronary artery bypass graft surgery] related TIMI major bleedings vs. clopidogrel'.

The graph compared patients treated with clopidogrel + ASA and Efient + ASA in relation to CV death, MI, stroke and days from randomization. Non-CABG TIMI major bleeds were also compared for the two groups. The graph included data from 0 – 450 days from randomization and a vertical dotted line labelled 'Recommended length of treatment' indicated what appeared to be 365 days. On the right hand side of the graph was a prominent downward arrow labelled '21% RRR' [relative risk reduction]. Beneath this the actual risk reduction (ARR) was given in much smaller type 'ARR = 2.4%' p=0.0221' in favour of Efient in relation to CV death, MI, stroke. The comparison of non-CABG TIMI major bleeds did not show a statistically significant difference (p=0.6451).

COMPLAINT

AstraZeneca alleged that the title of the graph referred to analysis of the primary efficacy endpoint and key safety endpoint at 15 months. While Montalescot *et al* supported this graph, Section 4.2 of the Efient SPC stated that it was recommended for use in adult patients up to 12 months only. This therefore promoted Efient beyond the terms of its licence and was misleading in breach of Clauses 3.2 and 7.2.

Further the graph illustrated a subgroup analysis of the primary endpoint, including RRR and ARR figures based on outcomes at 15 months. A faint dotted line was presented at 12 months showing the recommended (and therefore licensed) maximum duration of treatment, however the graph continued far beyond this point. This off-licence promotion of Efient was compounded by there being no presentation of the actual data, for example ARR and RRR figures, at the 12 month point. This created the overwhelming impression that Efient could and should be used in excess of the maximum licensed duration of treatment and constituted misleading and off-label promotion. Breaches of Clauses 7.2 and 3.2 were alleged.

AstraZeneca alleged that the graph demonstrated a subgroup analysis of a key safety endpoint of non-CABG TIMI major bleeds at 15 months, contrary to the maximum licensed recommended duration of treatment of 12 months in breach of Clause 3.2. In addition, the information was presented as showing no significant difference between Efient and clopidogrel. While this might be the case in this specific subgroup, in the overall TRITON-TIMI 38 study Efient demonstrated significantly higher rates of non-CABG TIMI major bleeding (2.4% vs 1.8%, p=0.03), life threatening bleeding (1.4% vs 0.9%, p=0.01) and fatal bleeding (0.4% vs 0.1%, p=0.002). There was no mention of overall results anywhere within the leavepiece to provide the necessary context for clinicians to make an informed decision in relation to these serious outcomes. AstraZeneca alleged that this was therefore inaccurate, misleading and concerning as such selective representation of the data in such a misleading way, to the clear benefit of Efient, did not reflect high standards being maintained. Breaches of Clauses 7.2, 7.9 and 9.1 were alleged.

RESPONSE

Daiichi-Sankyo and Lilly referred to Section 4.2 of the Efient SPC, Posology and method of administration, which stated that 'A treatment of up to 12 months is recommended, unless the discontinuation of Efient is clinically indicated'. The companies also referred to Section 5.1, Pharmacodynamic properties, which mentioned the study endpoints which were reached after a median follow up period of '14.5 months (maximum of 15 months with a minimum of 6 months follow-up)'. Reference to use of Efient beyond 12 months was also included in Section 4.8, Undesirable effects, which stated 'Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one clopidogrel-controlled study (TRITON) in which 6741 patients were treated with prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) for a median of 14.5 months (5802 patients were treated for over 6 months, 4136 patients were treated for more than 1 year)'.

Daiichi-Sankyo and Lilly submitted that the above sections of the SPC were key in the assessment and determination of the complaint and supported the companies' position that the promotion of Efient was in accordance with the terms of its marketing authorization and not inconsistent with the particulars listed in its SPC.

The companies noted that AstraZeneca conceded that the references supported the depiction of the data in the leavepiece. Other than the alleged breach of Clause 2, the allegations were limited to promoting Efient in breach of Clause 3 and consequently Clause 7.

Daiichi-Sankyo and Lilly submitted that the reference to the STEMI sub-group analysis primary endpoint in the leavepiece was consistent with the Efient SPC which explicitly referred to a maximum 15 month follow-up period in Section 5.1 and, as a consequence, was not in breach of Clause 3.

Section 4.2 of the Efient SPC stated that the *recommended* duration of therapy is up to 12 months (emphasis added). This recommendation was clearly shown four times in the leavepiece. Firstly, at the top of page 1, in bold font ('Recommended for up to 12 months'); secondly, on the graph on page 1 with a dotted line at 12 months, beneath the words 'Recommended length of treatment'; thirdly, on the Kaplan Meier curves on page 2 entitled 'TRITON-TIMI 38: Landmark analysis of time from first event to second event by randomised therapy' with a dotted line at 12 months, beneath the words 'Recommended length of treatment' and finally in the prescribing information on the back page.

Daiichi-Sankyo and Lilly submitted that the leavepiece at issue emphasised, and majored on, the recommended duration of therapy. References to the 15 month follow-up period were, in all cases, both in accordance with the Efient marketing authorization and not inconsistent with the particulars of its SPC (Clause 3) and, further, were positively required in order not to mislead (Clause 7.2) and with respect to the graph adapted from Montalescot *et al* in order to provide a clear, fair and balanced representation of the data in accordance with Clauses 7.8 and 7.6.

Daiichi-Sankyo and Lilly submitted that the leavepiece was not misleading, either directly or by implication or as a practical matter. Efient was launched in the UK in April 2009; the TRITON-TIMI 38 data had been used since that time, and the graph from Montalescot *et al* had been used in promotional materials since at least April 2009, each without challenge. The companies were not aware of any health professionals suggesting that they had been misled by the graphical depiction of the pre-specified STEMI subgroup analysis of TRITON-TIMI 38, as alleged by AstraZeneca, or at all.

Daiichi-Sankyo and Lilly drew support for their view from the European Society of Cardiology's two guidelines, which each recommend Efient for no longer than 12 months. Furthermore, it was the companies' understanding that UK cardiology/PCI centres that had Efient on formulary typically have set the maximum length of treatment as 12 months. The companies were not aware of anyone setting a treatment duration of more than 12 months. In a handful of cases, maximum length of therapy had been set at a much shorter period – as little as 1 month or even just the loading dose.

Most importantly, the companies had no evidence to suggest that Efient was prescribed for longer than the recommended duration of therapy of 12 months.

PANEL RULING

The Panel noted that Section 4.2 of the Efient SPC, Posology and method of administration, stated that 'A treatment of up to 12 months is recommended, unless the discontinuation of Efient is clinically indicated …'. The graph at issue on page one of the leavepiece included a dotted line labelled 'Recommended length of treatment' at what appeared to be 365 days from randomization. The calculations for RRR and ARR appeared to be at the end of the study, ie 15 months.

The Panel noted that Section 4.8 (Undesirable effects) and 5.1 (Pharmacodynamic properties) of the Efient SPC referred to data at 14.5 months.

Clause 3.2 required that promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in the SPC. The Panel noted that the 15 month data was taken from the TRITON-TIMI 38 study, a pivitol registration study for Efient. Study visits were conducted at hospital discharge, at 30 days, 90 days and 3 months intervals thereafter for a total of 6 to 15 months.

The Panel noted that the prespecified subgroup analysis on patients with STEMI stated that the TRITON-TIMI 38 study was not prospectively designed or powered to show superiority of prasugrel over clopidogrel in the STEMI cohort alone. The subgroup analysis included detailed results for major efficacy and safety endpoints at 30 days and 15 months. The primary endpoint was CV death, non-fatal myocardial infarction or non-fatal stroke. The subgroup analysis had not been carried out at 12 months.

The Panel considered that the 15 month data would be of interest to prescribers. The SPC clearly referred to data beyond 12 months. The Panel considered that whilst it was acceptable to refer to the SPC data such references should be secondary to the statement at Section 4.2 of the SPC that treatment of up to 12 months was recommended.

The Panel noted that although the dotted line on the graph did not state the actual length of treatment, it could be approximately determined from the x axis. Neither the dotted line on the graph, nor the strapline at the top of the page which included the phrase 'Recommended for 12 months' were a visually prominent part of the overall page design. The Panel did not consider that the material on the page in question could be qualified by references to 12 month data in subsequent pages or in the prescribing

information as suggested by the companies. The supplementary information to Clause 7, general, stated, *inter alia*, that claims in promotional material must be capable of standing alone regards accuracy etc. The heading in question 'Triton-TMI 38: pre-specified STEMI subgroup analysis of the primary efficacy endpoint* and key safety endpoint** at 15 months (n-3, 534)' appeared in a highlighted green box and was visually prominent. It made no mention of the recommended duration of treatment. The graph beneath depicted and analysed data at 450 days. The Panel considered that the heading was misleading about the recommended treatment period and consequently inconsistent with the SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel noted that the graph made claims in relation to primary efficacy outcomes at 15 months. Other than the lines on the graph there was no mention or presentation of the actual ARR, or any other data, at 12 months.

The Panel noted that whilst a dotted line on the graph represented the recommended treatment period by presenting the efficacy and safety results at 15 months prominently with no data at 12 months the graph in effect promoted Efient for 15 months treatment. The 15 month data was not secondary to and or placed within the context of the 12 month recommended treatment period. This was misleading and inconsistent with the SPC recommendation. Breaches of Clauses 3.2 and 7.2 were ruled.

In relation to the results for non-CABG TIMI major bleeds the Panel noted that the subgroup analysis showed no significant difference between clopidogrel + ASA and Efient + ASA (p=0.6451). The overall outcome in this regard in TRITON-TIMI 38 was statistically significant in favour of clopidogrel + ASA for the key safety endpoint (2.4% vs 1.8% p=0.03 for non-CABG related TIMI major bleeding). Further, the data for life threatening bleeding (1.4% vs 0.9% p=0.01) and fatal bleeding (0.4% vs 0.1% p=0.002) were also in favour of clopidogrel + ASA. Montalescot *et al* stated that compared with clopidogrel, Efient was not associated with any significant increase in major bleeding, life-threatening bleeding or major or minor bleeding; however, formal testing for interaction was negative and these data should be interpreted with caution. In addition, differences in age (people presenting with STEMI were on average 2 years younger than non STEMI participants), the lower proportion of women, fewer diabetics and more smokers were differences that could account in part for the recorded low bleeding risk in the STEMI cohort.

The Panel considered that the allegation that the graph demonstrated a subgroup analysis of non-CAGB TIMI major bleeds at 15 months contrary to the maximum licensed duration of treatment of 12 months was covered by its ruling of a breach of Clause 3.2 as set out above.

The Panel noted that the overall safety results had not been included and it considered that the subgroup analyses had not been placed in context. The balance of the evidence had not been presented. Breaches of Clauses 7.2 and 7.9 were ruled. As the data related to safety endpoints the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

2 Bar Chart and Graph on Page 2

Page 2 was headed 'Make A Difference Now to Protect Their Future'. A bar chart followed by a graph were presented on this page.

The main heading to the bar chart was 'Confidence To Reduce The Risk Of Stent Thrombosis vs. Clopidogrel'. This was followed by the bar chart at issue which was headed 'TRITON-TIMI 38: pre-specified STEMI subgroup analysis of the secondary efficacy endpoint of stent thrombosis at 15 months (n=3,534)'. The bar chart was adapted from Montalescot *et al* and compared the incidence of definite or probable stent thrombosis of Efient + ASA (n=1769) and clopidogrel + ASA (n=1765). A prominent downward arrow labelled '42% RRR' appeared above the Efient bar. The ARR of 1.2%, p=0.0232 was given in less prominent smaller font on the left hand side of the bar chart. The claim 'Efient significantly reduced the risk of stent thrombosis compared with clopidogrel' appeared alongside the heading on the left hand side of the bar chart.

The second half of the page was headed 'Confidence to Reduce Recurrent Cardiovascular Events vs. Clopidogrel' beneath which was the heading 'TRITON-TIMI 38: Landmark analysis of time from first event to second event by randomised therapy (n=1,203)' to the graph.

The graph showed data adapted from Murphy *et al* (2008) which compared primary endpoint events (CV death, non-fatal MI or non-fatal stroke) for Efient + ASA and clopidogrel + ASA for 450 days from first event to second event or last follow-up. A dotted line was given on the graph to show recommended length of treatment. The results at 450 days were given. A prominent downward arrow labelled '35% RRR' appeared adjacent to the graph above the smaller much less prominent figure 'ARR = 4.6% (p=0.016)'. The claim 'Among patients with an initial non-fatal cardiovascular event, Efient significantly reduced second events compared with clopidogrel' appeared alongside the graph.

COMPLAINT

AstraZeneca stated that the title and body of the bar chart referred to analysis of the secondary efficacy endpoint at 15 months. Whilst Montalescot *et al* supported this graph, Efient was recommended for use in adult patients up to a maximum of 12 months only. AstraZeneca alleged promotion beyond the licence, which was misleading in breach of Clauses 3.2 and 7.2.

With regard to the graph illustrating the endpoint of secondary CV events in the STEMI subgroup, AstraZeneca alleged that whilst Murphy *et al* supported the graph, the SPC recommended Efient for use in adult patients up to a maximum of 12

months only. Similarly, to the graph on page 1, this promoted beyond the licence and was misleading in breach of Clauses 3.2 and 7.2.

RESPONSE

Daiichi-Sankyo and Lilly submitted that the pre-specified STEMI subgroup analysis was performed at the pivotal study endpoint after a maximum duration of therapy of 15 months. It was consistent with Section 5.1 of the SPC and the companies did not consider that including it in the leavepiece was a breach of the Code.

Similarly, the companies submitted that the reference to 15 months in relation to recurrent cardiovascular events was consistent with Section 5.1 of the Efient SPC. To further emphasise the recommended length of therapy (Section 4.2), a dotted line at 12 months beneath the words 'Recommended length of treatment' was included.

PANEL RULING

The Panel noted its general comments at Point 1 above about the recommended treatment period; references in the SPC to the data for 14.5 months; that prescribers would be interested in the 15 month data set out in Point 1 above and that references to treatment beyond 12 months should be secondary to and placed within the context of 12 month treatment period at section 4.2 of the SPC. The Panel further noted that there was no prominent mention on page 2 that treatment up to 12 months was recommended.

In relation to the bar chart the Panel noted that the RRR claim for the risk of stent thrombosis was based on 15 month data. The Panel considered that the bar chart and its heading which referred to analysis at 15 months were inconsistent with the SPC and misleading. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel noted that Murphy *et al* looked at the recurrence of the primary endpoint events in TRITON-TIMI 38 with Efient compared with clopidogrel and concluded that Efient reduced both first and subsequent cardiovascular events at 15 months compared with clopidogrel in patients with ACS.

The Panel noted that the RRR claim for the advantage for Efient + ASA compared to clopidogrel + ASA was based on 15 month data. The Panel noted that the graph featured a dotted line at 12 months which represented the recommended treatment period. However by presenting the results at 15 months prominently the graph promoted the use of Efient for 15 months. This was misleading and inconsistent with the SPC recommendation. Breaches of Clauses 3.2 and 7.2 were ruled.

3 Page 3 was headed 'Compared with Clopidogrel, Efient Offers:

- **Consistent platelet inhibition in healthy subjects**
- **Superior, long-lasting CV protection for 12 months of therapy**
- **No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients'.**

COMPLAINT

AstraZeneca noted that the second bullet point highlighted that Efient should be used for 12 months. This bullet point was consistent with the SPC but in no way mitigated against the repeated off label promotion seen in the rest of the leavepiece with respect to duration of treatment.

The final bullet point again did not mention or reference the fact that in the main TRITON-TIMI 38 study, there were significantly worse bleeding rates seen with Efient vs clopidogrel. AstraZeneca alleged that this was not a balanced reflection of all available data, was misleading and did not reflect high standards, in breach of Clauses 7.2, 7.9 and 9.1.

In summary, AstraZeneca alleged that the leavepiece contained multiple misleading claims relating to efficacy and safety; promoted the off licence use of Efient; did not maintain high standards and did not accurately convey the incidence of serious side-effects seen with Efient by clearly providing the contradictory results of the main TRITON-TIMI 38 study. Given the repeated nature and totality of these issues, and particularly with respect to the last and most serious point, AstraZeneca alleged a reduction in confidence in the industry as a whole in breach of Clause 2.

In addition, AstraZeneca had also been made aware of a similar leavepiece, UKEFF00713, which focussed on the diabetes subgroup of the TRITON-TIMI 38 study. All of the issues and potential breaches of the Code highlighted with respect to UKEFF00714a also applied to this leavepiece. As previously mentioned, AstraZeneca believed that this approach had been adopted in a widespread manner across all promotional materials and asked the Authority to consider this when making its assessment.

AstraZeneca stated that despite unsuccessful inter-company dialogue, Daiichi-Sankyo and Lilly had indicated that they had withdrawn the leavepiece UKEFF00714a with immediate effect. AstraZeneca acknowledged this, though no broader agreement had been reached on the wide ranging concerns it had raised and which were detailed in its letter.

RESPONSE

Daiichi-Sankyo and Lilly stated that it appeared that AstraZeneca might have misunderstood the bullet point 'Superior, long-lasting CV protection for 12 months'. The statement was not a positive assertion/representation of Efient's licensed duration of therapy, it was intended to be a comparison of the two medicines, in compliance with Clause 7.

With regard to non-CABG TIMI major bleeding Daiichi-Sankyo and Lilly submitted that as an indication of efforts to amicably resolve the matter with AstraZeneca, it had offered to include the 15

month study endpoint non-CABG TIMI major bleeding results from the pivotal registration TRITON-TIMI 38 study in the leavepiece. As a consequence, the leavepiece in question was withdrawn to make changes.

Furthermore, the companies were prepared to emphasise even more clearly the recommended length of therapy of 12 months, whilst still depicting the 15 month pivotal registration trial data endpoints. Despite endeavours to make amends to the depiction of the graph, AstraZeneca was explicit in its position in that it 'would not find it acceptable to represent data for prasugrel beyond 12 months'. Daiichi-Sankyo and Lilly considered that there was no scientific or clinical merit to AstraZeneca's suggested approach of presenting 12 month post-hoc data from TRITON-TIMI 38: presenting data from a post-hoc analysis alone as demanded by AstraZeneca would be unacceptable and arguably in breach of Clause 7.8.

Daiichi-Sankyo and Lilly submitted that although not the subject of the original complaint, so far as was relevant, leavepiece UKEFF00713 was withdrawn in November 2011 as the item was not being used.

In the light of the above Daiichi-Sankyo and Lilly submitted that they had not breached the Code whether with respect to Clauses 2, 3 or 7, or at all.

With respect to the alleged breach of Clause 2, Daiichi-Sankyo and Lilly drew attention to the fact that the Montalescot graph was pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2009. No adverse comments were made about the graph. Although Daiichi-Sankyo and Lilly understood that such pre-vetting did not necessarily mean that the item complied with the Code, they believed that the MHRA, by endorsing the material, deemed the graph to be consistent with the Efient SPC. As a consequence the Daiichi-Sankyo's and Lilly's use of the leavepiece was not such as to be likely to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

PANEL RULING

The Panel noted its previous comments about the differences in outcomes between safety data in Montalescot *et al* and TRITION-TIMI in point 1 above. Whilst the claim 'No significant difference in non-CABG TIMI major bleedings in STEMI and diabetes patients' was an outcome of the subgroup analyses it did not reflect the authors caveats nor was it placed in the context of the outcomes of the TRITON-TIMI study as a whole. This was not a fair reflection of the data. Breaches of Clauses 7.2 and 7.9 were ruled. High standards had not been maintained in breach of Clause 9.1.

With regard to the alleged breach of Clause 2 in relation to the leavepiece as a whole the Panel noted that Clause 2 was used as a particular sign of censure and reserved for such use. The Panel considered that given its rulings, particularly those in relation to the presentation of safety data in Points 1 and 3 above, the circumstances warranted such a ruling and a breach of Clause 2 was ruled.

Complaint received **11 May 2012**

Cases completed **31 August 2012**