CASE AUTH/2016/7/07

NOVARTIS v BRISTOL-MYERS SQUIBB

Sprycel leavepiece

Novartis complained about a Sprycel (dasatinib) leavepiece issued by Bristol-Myers Squibb. Sprycel was indicated for use in patients with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including Novartis' product Glivec (imatinib).

Novartis stated that the four page spread of the leavepiece juxtaposed 'Selectivity' claims for Sprycel with claims about 'Sustainability' and 'Strength'. Under the 'Selectivity' heading Novartis noted the following bullet points: 'Sprycel also targets other oncogenic pathways such as c-KIT, Ephrin receptor kinase, PDHF ß receptor'; 'Sprycel is the first and only therapy to bind to both active and inactive conformations of the BCR-ABL'; 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*' and 'Sprycel is active against all BCR-ABL mutations tested, except T315I'. Whilst no specific efficacy claims were made, the juxtaposition of the 'Selectivity' section misleadingly implied that dasatinib's different mechanism of action referred to in the bullet points correlated with clinical benefits; however such implications were not supported by clinical data. Novartis further alleged that the subheading 'Sprycel has a different mechanism of action' was a hanging comparison.

Novartis noted that the selectivity page referred to three oncogenic pathways targeted by Sprycel and alleged that these could not be considered selective. Further more some of the pathways were specifically associated with tumours other than CML. The citing of dasatinib's targeted activity in respect to these pathways, under a heading of selectivity, next to claims on sustainability and strength of action, implied an unproven and unlicensed clinical activity in tumours expressing these pathways. At best this was misleading and at worst was promotion outside the Sprycel marketing authorization.

With regard to the bullet point 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', Novartis knew of no CML guidelines that cited the greater potency of dasatinib compared to imatinib as conferring superior efficacy. Furthermore, at the clinical doses prescribed, the superior potency *in vitro* of dasatinib did not confer any comparative benefits with respect to its side-effect profile (indeed, initial clinical data might suggest the contrary) nor its comparative cost with imatinib 400 or 600mg.

The Panel noted that the leavepiece was entitled 'Sprycel Chronic phase CML For imatinib resistant or intolerant patients'. Page 2 was headed 'Sprycel in Chronic phase', and pages 2, 3 and 4 all referred to imatinib resistant CML patients. It was thus in this context that page 5, headed 'Selectivity', would be read.

The Panel did not consider that, grammatically, the claim 'Sprycel has a different mechanism of action' was a hanging comparison. Further, the Panel considered that given the content of the previous pages, and the title of the leavepiece, it would be obvious to the reader that the claim compared Sprycel with imatinib. No breach of the Code was ruled.

The Panel noted that the claim 'Sprycel also targets other oncogenic pathways such as: c-KIT, Ephrin receptor kinases, PDGF ß receptor' was referenced to the summary of product characteristics (SPC). Section 5.1 stated that dasatinib inhibited the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases and PDGF ß receptor. Although such pathways were implicated in malignancies other than CML the claim at issue was in a leavepiece specifically targeted at CML. Given the context in which it appeared the Panel did not consider that the claim implied that Sprycel had clinical activity in any condition other than CML. The claim was neither misleading in that regard and nor did it promote the use of Sprycel beyond its SPC. The Panel considered that whilst the page was headed 'Selectivity' there was no actual claim that Sprycel was selective. Another page stated, beneath the heading 'Selectivity' that Sprycel offered a new multi-targeted mechanism of action. No breach of the Code was ruled.

The Panel noted that the subheading 'Sprycel has a different mechanism of action' was asterisked to the footnote, 'Based on *in vitro* data' which appeared in small, grey typeface, at the bottom of the page. The Panel considered that, except for 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', it was not clear from the outset that all the other claims at issue were based on *in vitro* data. Readers would assume that they related to the clinical situation which was not so. No data had been submitted to show the relevance of the claims to clinical practice. Bristol-Myers Squibb had submitted that the bullet points on page 5 'listed the possibilities' with regard to the product's mechanism of action. This was not entirely clear from the leavepiece. The Panel considered that, given the context in which they were made, the claims 'Sprycel is the first and only therapy to bind to both active and inactive conformations of BCR-ABL' and 'Sprycel is active against all BCR-ABL mutations tested, except T315I' were misleading as alleged; both were ruled in breach of the Code.

The Panel noted that the claim 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*' was not a claim for superior potency in relation to weight as alleged. Nonetheless, Bristol-Myers Squibb had not submitted any data to show what relevance this *in vitro* data had in clinical practice. The company submitted that it was one of a number of possible mechanisms of action for Sprycel which might explain its efficacy in imatinib resistant patients. The Panel did not consider this was entirely clear from the leavepiece as noted above. The clinical relevance of the data was not sufficiently clear to the reader. The Panel considered that the claim was misleading in this regard. A breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd complained about a leavepiece (ref DAS/1106/0146/1008) for Sprycel (dasatinib) issued by Bristol-Myers Squibb Pharmaceuticals Limited. Sprycel was indicated for use in patients with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including Novartis' product Glivec (imatinib).

The leavepiece at issue was folded concertina like and unfolded to reveal eight 'pages'. The four pages on one side of the leavepiece were successively headed 'Sprycel in Chronic Phase', 'Strength', 'Sustainability' and 'Selectivity'. It was the last page headed 'Selectivity' which was the subject of complaint.

Bristol-Myers Squibb voluntarily withdrew the leavepiece in April 2007 and informed Novartis by email on 12 April.

COMPLAINT

Novartis stated that the Sprycel leavepiece described the features of the product in an open 4-page spread which juxtaposed 'Selectivity' claims for the product with 'Sustainability' and 'Strength' claims. Whilst no specific efficacy claims were made in the 'Selectivity' section, the juxtaposition of this section was misleading as it implied that dasatinib's different mechanism of action correlated with clinical benefits; however this claim was not supported by clinical data. Furthermore, the subheading 'Sprycel has a different mechanism of action' appeared to be a hanging comparison, in breach of Clause 7.2 of the Code as no comparative data was presented in support.

The second bullet point on the 'Selectivity' page, 'Sprycel also targets other oncogenic pathways such as:' presented three biological features related to dasatinib, which targeted other oncogenic pathways c-KIT, ephrin receptor kinases and PDGF ß receptor. This claim was a non-sequitur from the heading 'Selectivity'. By definition, targeting three oncogenic pathways could not be considered selective.

Whilst these biological features were certainly of biological relevance, the bulleted points were unsupported by any reference to clinical data generated with dasatinib in tumours specifically expressing, for example, c-KIT (such as gastro-intestinal stromal tumours). Novartis acknowledged that the lack of a marketing authorization for Sprycel in tumours where these other oncogenic pathways were implicated absolutely prohibited any promotion of its therapeutic use in these tumour types. That said, the citing of dasatinib's targeted activity in respect to these three pathways, under a heading of selectivity, and then juxtaposed with sustainability and strength of action, implied either overtly or covertly, and deliberately or inadvertently, an unproven and unlicensed clinical activity in tumours expressing these pathways. At best this was misleading and at worst constituted promotion outside the Sprycel marketing authorization and a breach of Clause 3.2 was alleged.

The third bullet point under the heading 'Selectivity' stated 'Sprycel is the first and only therapy to bind to both active and inactive conformations of the BCR-ABL'. Whilst chemically this might currently be true, it implied that this structural feature conferred clinical benefit. However, no correlation had been clinically proven between the clinical activity of dasatinib and its binding profile. As the leavepiece failed to make this point clear, this statement was alleged to be misleading in breach of Clause 7.2.

With regard to the fourth bullet point 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', Novartis noted the supplementary information to Clause 7.2 which stated: 'Claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked with some practical advantage, for example, reduction in side-effects or cost of effective dosage'.

In this context, Novartis knew of no CML guidelines that cited the greater potency of dasatinib compared to imatinib as conferring superior efficacy. Furthermore, at the clinical doses prescribed, the superior potency *in vitro* of dasatinib most certainly did not confer any comparative benefits with respect to its side-effect profile (indeed, initial clinical data might suggest the contrary) nor its comparative cost with imatinib 400 or 600mg. Novartis alleged that the claim was in breach of Clause 7.2.

The last bullet point on the 'Selectivity' page, 'Sprycel is active against all BCR-ABL mutations tested, except T315I' presented the same issues as those set out above in that the claim implied a clinical benefit but with no clinical data presented in imatinib-resistant patients due to non-T315I mutations. Novartis thus alleged that the claim was misleading by inference, in breach of Clause 7.2.

RESPONSE

Bristol-Myers Squibb explained that CML was an unusual leukaemia in that it was associated with a specific chromosomal abnormality, the Philadelphia chromosome. This abnormal chromosome contained an aberrant fusion oncogene called BCR-ABL. This gene encoded the Bcr-Abl oncoprotein, which was a tyrosine protein kinase and which was believed to be both necessary and sufficient for the onset of this malignant condition. The treatment of CML was revolutionised

by the introduction of imatinib several years ago. Until then the existing therapies (such as hydroxyurea and interferon-alpha) were only partially successful in controlling the disease. Bone marrow transplantation (BMT) was a potential cure but the mortality associated with it was such that it was reserved only for the most fit of patients. Most CML patients were older than 60 years of age and were generally not fit for BMT.

Imatinib was a tyrosine kinase inhibitor specifically targeted against the Bcr-Abl oncoprotein. It led to lasting clinical and cytogenetic responses and greatly improved patients' quality of life. Unfortunately, some patients proved resistant to its effect and others proved intolerant of imatinib. The resistance could be primary resistance (ie that a patient upon first exposure to imatinib did not respond) or secondary resistance (ie that a patient initially responded to imatinib but eventually relapsed). The reasons for resistance to imatinib were multi-factorial and included mutations in the tyrosine kinase domain of the BCR-ABL gene and over-expression of the BCR-ABL gene. There were also BCR-ABL independent mechanisms of resistance. These latter mechanisms included clonal evolution, where the need for molecular drive by Bcr-Abl was circumvented and also mechanisms that altered the intracellular concentrations of imatinib, for example by the over-expression of efflux pumps.

Accordingly, there was still an unmet medical need for CML patients resistant or intolerant to imatinib. Sprycel was developed to address this need. It was licensed in November 2006 for 'adults with chronic, accelerated or blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib mesilate'.

The leavepiece was intended to be left with health professionals following an introductory discussion on Sprycel with Bristol-Myers Squibb representatives. It was a two-sided item but was folded in a manner which created four pages on either side.

Page 1 was the 'title' page. Upon opening the folded leavepiece and turning over from the title page, then pages 2, 3, 4, and 5 became apparent. The page at issue, page 5, was headed 'Selectivity' and was to be read in the context of the three other pages (2, 3, and 4, headed 'Sprycel in Chronic Phase', 'Strength' and 'Sustainability', respectively).

Pages 2, 3 and 4 introduced the CML indication for Sprycel and noted that Sprycel represented the first treatment for imatinib resistant or intolerant patients. The clinical efficacy of dasatinib in such patients was displayed in pages 3 and 4.

With regard to the claim 'Sprycel has a different mechanism of action' Bristol-Myers Squibb noted that the mechanism of action of a medicine was an allowable item to be addressed in any leavepiece and was an especially important element in a leavepiece which introduced a new medicine designed to overcome a deficiency in an existing well-established one.

Manifestly, if a new medicine was specifically designed and clinically proven to overcome resistance to an established one, then the new medicine must be acting in a different way. If the new medicine had exactly the same mechanism of action, then it would not be expected to overcome the resistance engendered to the established medicine. Stating that Sprycel had a different mechanism of action was thus an important point of education.

It was clear from the layout of the leavepiece (ie that page 5 was to be viewed in conjunction with pages 2, 3, and 4) and from the content of pages 2, 3 and 4 that Sprycel's mechanism of action was being compared with that of imatinib. The grammatical form of a 'hanging comparison' was wording such as 'better' or 'stronger'. The claim at issue was not of this form. Accordingly, Bristol-Myers Squibb denied that this claim was a hanging comparison and denied that it was in breach of Clause 7.2.

Sprycel had been shown in clinical studies to be effective in patients with imatinib resistance. The clinical studies leading to the grant of the marketing authorization included patients with imatinib resistance irrespective of the presumed cause of the resistance. Some of the key efficacy results of these studies were summarised in this leavepiece.

The five bullet points on page 5 listed the known pharmacology of dasatinib which in sum explained its ability to be effective in CML patients resistant to imatinib. It should be remembered, therefore, when considering the individual allegations below, that Sprycel's multiple mechanisms of action were such that, collectively, they were responsible for the product's efficacy against the possible multiple reasons for imatinib resistance.

With regard to the allegations about the claim 'Sprycel also targets other oncogenic pathways such as:' Bristol-Myers Squibb reiterated that there were many possible mechanisms for resistance to imatinib and it was difficult to determine which precise mechanism (or combination of mechanisms) was responsible in any one patient. In approximately half of patients, it was generally accepted that the most likely cause of resistance was point mutations of the BCR-ABL gene such that the local topology of the Bcr-Abl oncoprotein was altered at the molecular level, meaning that imatinib could no longer bind with adequate affinity and thus no longer inhibit oncoprotein activity. However, no such obvious reason was apparent for the remainder of resistant CML patients.

Accordingly, for a single medicine to be effective in a patient with imatinib resistance, it must be able to counter the effects of mutations but must also be able to act against the many other possible causes.

In *in vitro* tests, dasatinib had been shown to have a range of pharmacological activities. These included being a tyrosine kinase inhibitor. Indeed, *in vitro* tests showed it to be 325 times more potent than imatinib in inhibiting BCR-ABL. It was also an SRC kinase inhibitor and was active in a range of other oncogenic

pathways as shown in the leavepiece. It had been shown to be active against a wide range of BCR-ABL mutations (but not the T315I mutation). Whilst Bristol-Myers Squibb could acknowledge that certain of dasatinib's mechanisms of action might be pertinent to non-CML indications, the possible mechanisms of action of dasatinib listed in this leavepiece had the potential to counter certain possible mechanisms of imatinib resistance in CML, particularly in advanced disease.

Accordingly, in a CML leavepiece explaining the pharmacology of the product, it was pertinent to refer to these possible mechanisms of action, even though they might also have some meaning in other disease contexts.

Since all of the listed mechanisms had pertinence to CML, and appeared in a leavepiece which only referred to CML, Bristol-Myers Squibb refuted the allegation of promotion outside of Sprycel's licence, and denied any breach of Clause 3.2.

Bristol-Myers Squibb noted that Novartis accepted the validity of the underlying molecular biology of the claim 'Sprycel is the first and only therapy to bind to both the active and inactive conformations of BCR-ABL'. As above, this was but one possible mechanism of action for Sprycel which might explain its efficacy in imatinib resistant patients, and it was not presented as being wholly responsible for its clinical efficacy in these patients. That this was the case was apparent from the layout of the text on page 5. The subheading referred to 'mechanism of action' and then there were bullet points, including this one, which listed the possibilities.

Bristol-Myers Squibb noted that Novartis quoted the supplementary information to Clause 7.2 which cautioned that 'claims for superior potency in relation to weight are…best avoided unless they can be linked with some practical advantage, for example, reduction in side-effects or cost of effective dosage' (emphasis added by Bristol-Myers Squibb). However, the claim 'Sprycel is 325 fold more potent than imatinib' was not a claim for superior potency 'in relation to weight', and so did not represent the type of claim to which this section of the supplementary information was addressed.

Bristol-Myers Squibb referred to the superior potency of Sprycel in inhibiting BCR-ABL *in vitro* because this was but one of a number of possible mechanisms of action for Sprycel, which might explain its efficacy in imatinib resistant patients. The context of the statement did not suggest this particular mechanism of action of Sprycel should be considered in isolation to be wholly responsible for its clinical efficacy in patients with imatinib resistance. That this was the case was apparent from the layout of the text on page 5. There was a heading relating to 'mechanism of action' and then there were bullet points, including this one, which listed the possibilities.

Bristol-Myers Squibb noted that Novartis had further alleged that the claim 'Sprycel is 325 fold more potent than imatinib' implied that dasatinib had superior efficacy to imatinib and that there were no comparative benefits with respect to side-effect profile or cost.

Dasatinib had been proven, within its licensed indication, to be effective when a patient had imatinib resistance. Also, there was no cross-intolerance between imatinib and dasatinib meaning that dasatinib was a suitable treatment for patients who developed intolerance to imatinib. Bristol-Myers Squibb did not consider that cost was relevant to this allegation of a breach of Clause 7.2, but it should be noted that Sprycel was able to be used when patients developed resistance on 800mg/day of imatinib. The cost of 800mg of imatinib was more than the daily cost of Sprycel.

As above, the purpose of the claim 'Sprycel is active against all BCR-ABL mutations tested except T315I' was to inform of but one possible mechanism of action for Sprycel which might explain its efficacy in imatinib resistant patients. The context of the statement did not suggest that this particular mechanism of action of Sprycel should be considered in isolation to be wholly responsible for its clinical efficacy in patients with imatinib resistance. That this was the case was apparent from the layout of the text on page 5. There was a heading relating to 'mechanism of action' and then there were bullet points, including this one, which listed the possibilities.

Bristol-Myers Squibb denied all allegations of a breach of Clause 7.2.

PANEL RULING

The Panel noted that the leavepiece was entitled 'Sprycel Chronic phase CML For imatinib resistant or intolerant patients'. Page 2 was headed 'Sprycel in Chronic phase', and pages 2, 3 and 4 all referred at some point to imatinib resistant CML patients. It was thus in this context that page 5, headed 'Selectivity' would be read.

The Panel did not consider that, grammatically, the claim 'Sprycel has a different mechanism of action' was a hanging comparison. Further, the Panel considered that given the content of the previous pages, and the title of the leavepiece, it would be obvious to the reader that the claim compared Sprycel with imatinib. No breach of Clause 7.2 was ruled.

The Panel noted that the claim 'Sprycel also targets other oncogenic pathways such as: c-KIT, Ephrin receptor kinases, PDGF ß receptor' was referenced to the summary of product characteristics (SPC). Section 5.1 stated that dasatinib inhibited the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases and PDGF ß receptor. The Panel noted the submission by Novartis, and the acceptance by Bristol-Myers Squibb that such pathways were implicated in malignancies other than CML. Nonetheless the claim at issue was made in a leavepiece specifically targeted at CML. Given the context in which it appeared the Panel did not consider

that the claim implied that Sprycel had clinical activity in any condition other than CML. The claim was neither misleading in that regard and nor did it promote the use of Sprycel beyond its SPC. The Panel considered that whilst the page was headed 'Selectivity' there was no actual claim that Sprycel was selective. Another page stated, beneath the heading 'Selectivity' that Sprycel offered a new multi-targeted mechanism of action. No breach of Clause 3.2 was ruled.

The Panel noted that the subheading 'Sprycel has a different mechanism of action' was asterisked to the footnote, 'Based on *in vitro* data' which appeared in small, grey typeface, at the bottom of the page. The supplementary information to Clause 7 of the Code stated that in general claims should not be qualified by the use of footnotes and the like. Further, the supplementary information to Clause 7.2 stated that data derived from, *inter alia*, *in vitro* studies should be used with care so as to not mislead as to its significance.

The Panel considered that, except for 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', it was not clear from the outset that all other claims on page 5 regarding selectivity were based on *in vitro* data. Readers would assume that they related to the clinical situation which was not so. Bristol-Myers Squibb had not submitted any data to show the relevance of the claims to clinical practice. Bristol-Myers Squibb had submitted that the bullet points on page 5 'listed the possibilities' with regard to the product's mechanism of action. This was not entirely clear from the leavepiece. The Panel considered that, given the context in which they were made, the claims 'Sprycel is the first and only therapy to bind to both active and inactive conformations of BCR-ABL' and 'Sprycel is active against all BCR-ABL mutations tested, except T315I' were misleading as alleged; both were ruled in breach of Clause 7.2.

The Panel noted that the claim 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*' was not a claim for superior potency in relation to weight as alleged. Nonetheless, Bristol-Myers Squibb had not submitted any data to show what relevance this *in vitro* data had in clinical practice. The company submitted that it was one of a number of possible mechanisms of action for Sprycel which might explain its efficacy in imatinib resistant patients. The Panel did not consider this was entirely clear from the leavepiece as noted above. The clinical relevance of the data was not sufficiently clear to the reader. The Panel considered that the claim was misleading in this regard. A breach of Clause 7.2 was ruled.

Complaint received	**6 July 2007**
Case completed	**28 August 2007**