CASE AUTH/3675/7/22

COMPLAINANT v NOVARTIS

Allegations regarding promotion of Jakavi (ruxolitinib phosphate) on digital media

CASE SUMMARY

This case was in relation to a number of concerns related to claims made on the Jakavi webpage on the Novartis UK health professional website.

The Panel ruled a breach of the following Clauses of the 2021 Code because:

- **it considered that the claim 'Improved survival benefit compared with BAT' would likely imply to a busy health professional that Jakavi had shown a statistically significant benefit in relation to survival compared with BAT, which was not so and was thus misleading; in the Panel's view, the footnote in smaller font beneath the 'Footnotes & references' heading did not negate this misleading impression. It considered, noting the results of COMFORT-II, that the misleading impression, created by the 'Improved survival benefit compared with BAT' claim, could not be substantiated, and a breach of Clause 6.2 was ruled.**

Breach of Clause 6.1	**Making a misleading claim**
Breach of Clause 6.2	**Making an unsubstantiated claim**
Breach of Clause 5.1	**Failing to maintain high standards**

The Panel ruled no breach of the following Clause of the 2021 Code because it noted its ruling of Clause 5.1 above, which it considered adequately covered the matter:

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

The Panel ruled no breach of the following Clauses of the 2021 Code in relation to the claim 'The day you choose Jakavi (ruxolitinib) is the day you could change their life' because it considered that readers would likely interpret the claim as the day the decision was made to prescribe Jakavi would be the day a patient's life could start to change; it did not imply Jakavi would show a clinical benefit and change an individual's life within a day as alleged:

No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
No Breach of Clause 6.2	**Requirement that claims/information/comparisons must be capable of substantiation**

The Panel ruled no breach of the following Clauses of the 2021 Code because:

- **It did not consider that including the 'survival' box in the context of the 'Response', 'Control', 'Survival' graphic was a hanging comparison as alleged**
- **Whilst in its view there was a difference between showing improved survival versus another treatment and improved survival versus placebo, there was nonetheless evidence to show a survival benefit for Jakavi compared with placebo which was statistically significant:**

No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
No Breach of Clause 6.2	**Requirement that claims/information/comparisons must be capable of substantiation**
No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

The Panel, ruled no breach of the following Clauses of the 2021 Code because the complainant had not provided any evidence to demonstrate that 'well characterised' gave the impression that Novartis had stated Jakavi was 'safe' as alleged:

No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
No Breach of Clause 6.2	**Requirement that claims/information/comparisons must be capable of substantiation**
No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from an anonymous, contactable complainant who described themselves as a health professional and later became non-contactable.

COMPLAINT

The complainant provided a link (link provided) and submitted that a number of claims were untrue for the promotional marketing of Jakavi (ruxolitinib phosphate) on digital media. The complainant explained that there was a claim at the top of the page above the image of two people, which claimed, 'The day you choose Jakavi is the day you could change their life'. This was too broad ranging a claim as it was simply saying that the medicine would be life-changing, despite there being no evidence to confirm the medicine had changed someone's life in a day. The complainant stated even if someone was initiated on Jakavi, the patient would have to

tolerate the medication and it would be a long time before any clinical benefit vs a day. In addition, survival as a yellow box was presented next to the image but there was no statistically significant data to demonstrate survival and the term 'survival' was a hanging comparison according to the complainant; the complainant alleged breaches of Clause 6.1, 6.2, 5.1 and 2 of the 2021 Code in relation to this claim. The complainant stated further down the page, there were 4 boxes. One of these was improved survival benefit compared to best available treatment (BAT). The 'survival benefit' was in bold to stand out to the reader. The complainant alleged this was totally wrong as the paper that this claim was taken from demonstrated p=0.06 (not significant, for descriptive purposes only). As the significance had failed, it concerned the complainant that such a claim had been put forwards without any note about the p-value score; breaches of Clauses 6.1, 6.2, 5.1 and 2 were alleged. Another box claimed Jakavi had a well-characterised safety profile. This was not true as Jakavi had a whole range of side-effects which were very common. These included life-threatening side-effects, such as sepsis and neutropenia to name a few. Considering such side-effects, the complainant stated it was shocking that a claim that the medication was well-characterised had been made which had connotations that medication was safe; the complainant alleged breaches of Clauses 6.1, 6.2, 5.1 and 2. The complainant stated such false claims were very concerning and risked being able to provide the most rational treatment choice to a patient.

RESPONSE

Novartis submitted that it was concerned to receive the complaint, which had been taken very seriously. The complaint alleged that Novartis Pharmaceuticals UK Limited had committed a number of breaches of the 2021 ABPI Code of Practice for the Pharmaceutical Industry in the context of the promotion of Jakavi on digital media, the allegations of which Novartis addressed in its response under the headings below.

1 Statement 'The day you choose Jakavi® (ruxolitinib) is the day you could change their life' and yellow 'survival' box

The complaint referred to the banner image which was presented on the Jakavi (ruxolitinib) page on the Novartis UK health professional website.

The webpage was published in February 2022. It was directed to, and was accessible to, health professionals in the United Kingdom. The webpage displayed a pop-up gateway to ensure that members of the public did not inadvertently access the webpage. To access the webpage, a health professional could:

i) find the webpage by conducting a search for Jakavi on a search engine;
ii) access the link to the webpage directly, where this had been provided to the user; or
iii) navigate from the homepage (health.novartis.co.uk) and select 'Medicines' on the webpage menu bar, and then select Jakavi® (ruxolitinib) under the heading 'Haematology'.

The webpage was certified by a registered UK pharmacist and a copy of the certificate was provided.

Novartis noted that the complainant alleged that the banner image on the webpage made a broad claim, by stating 'The day you choose Jakavi® is the day you could change their life'. Specifically, the complainant alleged that this was stating that the medicine would be life-

changing, despite there being no evidence to confirm the medicine had changed someone's life in a day. Additionally, the complainant alleged that there was no statistically significant data to demonstrate survival, and by including the yellow 'survival' box as part of the image, this was a hanging comparison. Novartis addressed both points under the headings below.

i) Statement

Novartis disagreed with the complainant. Firstly, the statement present on the image did not claim that Jakavi would change an individual's life in one day, as suggested by the complainant. The statement provided that the day Jakavi was chosen as a treatment, was the day in which the prescribing decision was made, and the prescribing decision '*could*' change a patient's quality of life in the long-term on treatment. Novartis emphasised that the word 'could' had been included in this statement, which was to highlight the possibility of this happening, rather than it being a statement of fact. References 1-3, which were referred to on the banner image, could clearly substantiate the statement, as set out below.

Reference 1 – Section 5.1 of the Jakavi SPC was based on two randomised phase 3 studies (COMFORT-I and COMFORT-II) that were conducted in patients with Myelofibrosis (MF) (primary MF, post-polycythaemia vera MF or post-essential thrombocythaemia MF). A significantly higher proportion of patients in the Jakavi group achieved ≥35% reduction from baseline in spleen volume (Table 7 of the SPC), regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary MF, post-polycythaemia vera MF, post-essential thrombocythaemia MF).

The probability of maintaining spleen response (≥35% reduction) to Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using Myelofibrosis Symptom Assessment Form (MFSAF) diary v2.0), as compared to 5.3% in the placebo group ($p<0.0001$ using chi-square test). The mean change in the global health status at week 24, as measured by the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ C30), was +12.3 for Jakavi and -3.4 for placebo ($p<0.0001$).

Reference 3 – Harrison C, *et al*. N Engl J Med. 2012;366:787-798 concluded that 'Continuous ruxolitinib therapy, as compared with the best available therapy, was associated with marked and durable reductions in splenomegaly and disease-related symptoms, improvements in role functioning and quality of life, and modest toxic effects. An influence on overall survival has not yet been shown'.

ii) Survival Box

Novartis disagreed with the complainant. The purpose of the banner image (where the survival box was a part of the image) was to highlight the benefit of using Jakavi. The references 1-3 included on the image substantiated the statement being made, which Novartis addressed in detail below. There was no comparison being made on the banner, nor was one being suggested. Novartis believed that the complainant was creating a sense of comparison where none was present. Novartis discussed the survival outcome data at a later stage below on the webpage (and under heading 2 of this complaint response).

In light of this, for (i) and (iii) above, Novartis had not acted in breach of Clauses 5.1, 6.1, 6.2 and 2 of the Code.

2 'Survival benefit' and 'Well-characterised safety profile' boxes

On the webpage, following the first paragraph, there were four boxes. The complainant alleged that:

i) the box with 'survival benefit' had these words in bold to stand out to the reader, and that this was wrong as the paper the claim was taken from demonstrated p=0.06 and as the significance had failed, it was concerning that such a claim had been put forwards without any notice about the p-value score (the '**Survival Benefit Box**'); and

ii) the box with 'well-characterised safety profile' claimed Jakavi had a well-characterised safety profile, and this was not true as Jakavi had a 'whole range of side effects which were very common, including life threatening side effects such as a sepsis and neutropenia'. Claim that medication was well-characterised had connotations that medication was safe (the '**Safety Profile Box**').

In both (i) and (ii) the complainant alleged that Novartis had acted in breach of Clauses 6.1, 6.2, 5.1 and 2 of the Code.

Novartis disagreed with the complainant in both instances.

With regard to the 'Survival Benefit Box', despite the assertion of the complainant that there was no note about the p-value score present, this was included in the third footnote of the webpage.

Additionally, it was stated in Section 5.1 of the Jakavi SPC (Reference 1) that the results of both the COMFORT 1 and COMFORT 2 studies, which clearly substantiated a survival benefit, in particular:

- 'In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.
- In COMFORT-I, after a median follow–up of 61.7 months, the death rate in patients randomised to the ruxolitinib arm was 44.5% (69 of 155 patients) versus 53.2% (82 of 154) in patients randomised to placebo. There was a 31% reduction in the risk of death in the ruxolitinib arm as compared to placebo (HR 0.69; 95% CI 0.50-0.96; p=0.025).
- In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythaemia vera and post essential thrombocythaemia subgroup.
- In COMFORT-II, after a median follow-up of 55.9 months, the death rate in patients randomised to the ruxolitinib arm was 40.4% (59 of 146 patients) versus 47.9% (35 of 73 patients) in patients randomized to best available therapy (BAT). There was a

> 33% reduction in risk of death in the ruxolitinib arm compared to the BAT arm (HR 0.67; 95% CI 0.44-1.02; p=0.062).'

Reference 7 on the 'Survival Benefit Box' was an article which highlighted that of the 219 patients evaluated during the course of the COMFORT-II study, 146 patients were randomised to ruxolitinib and 73 patients were randomised to BAT. After the primary analysis at week 48, all patients remaining on study entered into the extension phase, including 45 patients initially randomised to BAT who crossed over to receive ruxolitinib (median time to crossover by K-M estimate, 75 weeks). At study completion, 39 patients (26.7%) in the ruxolitinib arm and 11 of the 45 patients (24.4%) who crossed over from the BAT arm to receive ruxolitinib completed 5 years of on-study treatment; these patients were still receiving treatment benefit and were offered commercially available ruxolitinib or enrolment in the compassionate use program following completion of the trial.

Additionally, overall, 59 (40.4%) and 35 (47.9%) deaths were reported in the ruxolitinib and BAT arms, respectively. Median overall survival (OS) was not reached in the ruxolitinib arm and was 4.1 years in the BAT arm. In the intention-to-treat (ITT) analysis, patients randomized to ruxolitinib had longer OS compared with those randomized to BAT, with a 33% reduction in risk of death with ruxolitinib treatment hazard ratio (HR), 0.67 (95% confidence interval (CI), 0.44–1.02); P=0.06); the K-M estimated probability of survival at 5 years was 56% with ruxolitinib and 44% with BAT. However, the confounding effect on OS of crossover from BAT to ruxolitinib became apparent in this extended follow-up compared with previous analyses (ervantes F, Vannucchi AM, Kiladjian JJ, Al-Ali HK, Sirulnik A, Stalbovskaya V *et al*. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood 2013; 122: 4047–4053) and (Cervantes F, Kiladjian JJ, Niederwieser D, Sirulnik A, Stalbovskaya V, McQuitty M *et al*. Long-term efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for the treatment of myelofibrosis. Blood 2012; 120: abstract 801). After adjustment was re-censored in the rank preserving structural failure time (RPSFT) model, the number of deaths in the BAT group was 32, with a median survival of 2.7 years, and the crossover-corrected HR for OS was 0.44 (95% CI, 0.18–1.04) in favor of ruxolitinib vs BAT.

Given the level of crossover, Novartis' strong view was that the data available and referenced on the webpage clearly substantiated a survival benefit of Jakavi. This was also highlighted in the conclusion by the author of the COMFORT-II article (Reference 3, on the webpage):

> *'A survival advantage was apparent in patients randomized to ruxolitinib compared with patients randomized to BAT (median not reached vs median of 4.1 years with BAT), despite the majority of BAT patients crossing over to receive ruxolitinib during the course of the study. This observation indicates a plausible clinical and survival advantage with earlier treatment.'*

The crossover clearly had an influence on the p-value; however, Novartis maintained that the data clearly indicated an improved survival benefit in comparison with BAT as indicated in both the SPC and the References 1-3 on the webpage.

With regard to the 'Safety Profile Box', Novartis did not state that Jakavi was a safe medication as the complainant alleged. The statement 'well-characterised' meant that the characteristics of the safety profile were well known and the reference (Jakavi SPC) on the 'Safety Profile Box' highlighted what these characteristics were in detail. In particular, Section 4.8 of the SPC

highlighted a well-known safety profile that had been studied for over fifty months in the COMFORT-II study. Jakavi was not a new medication, and most importantly, was not in a list of additional monitoring. For these reasons, Novartis disagreed with the complainant as the safety profile was well-characterised and the words 'well-characterised' did not have connotations of, or suggest that, the medication was safe.

For the reasons set out above, Novartis had not acted in breach of Clauses 5.1, 6.1, 6.2 and 2 of the Code with respect to the complainant's concerns regarding the 'Survival Benefit Box' and 'Safety Profile Box'.

PANEL RULING

The Panel noted the complaint was in relation to the Jakavi webpage on the Novartis UK health professional website.

The top of the webpage included a banner which contained the statement 'The day you choose JAKAVI (ruxolitinib)' followed by 'is the day you could change their life' in smaller font below. Below this were two sets of images of a male and a female on a sofa – one image of the male and female was greyed out and appeared to depict worried/concerned individuals comforting each other; next to this image was what appeared to be the same male and female depicted in colour laughing with one another and eating. Next to the image were 3 coloured boxes containing the words 'Response', 'Control', 'Survival'.

Below the image was a link to the prescribing information and the licenced indication for Jakavi. and to the side of this text a number of links related to 'improving patient outcomes', 'Optimising Jakavi dosing', 'Safety profile', 'Real world insights', 'Resources', and 'Contact us'. Below this were four boxes titled:

- Recommended by **BSH guidance** and reimbursed across the UK.
- Treating with **Jakavi can help reduce** a patient's **spleen size** and **symptom burden**.
- Improved **survival benefit** compared with BAT.
- **Well-characterised** safety profile.

Below these boxes it stated 'Jakavi is the only JAK inhibitor approved for MF with up to 5 years follow up data'.

The Panel noted there were a number of footnotes and references.

The Panel noted the complainant's allegation that the claim 'The day you choose Jakavi is the day you could change their life' was too broad and gave the impression the medicine would be life changing despite there being no evidence to confirm the medicine changed someone's life in a day; a patient would need to tolerate the medicine and it would be a long time before any clinical benefit could be seen.

In the Panel's view, the claim 'The day you choose Jakavi (ruxolitinib) is the day you could change their life' did not imply Jakavi would show a clinical benefit and change an individual's life within a day as alleged; the Panel considered readers would instead likely interpret the claim as the day the decision was made to prescribe Jakavi would be the day a patient's life could start to change and the Panel therefore, based on the complainant's narrow allegation, ruled **no breach of Clauses 6.1 and 6.2**.

With regard to the 3 coloured boxes containing the words 'Response', 'Control', 'Survival', the Panel noted the complainant's concern that survival as a yellow box presented next to the image described above was a hanging comparison and there was no statistically significant data to demonstrate survival.

The Panel noted Novartis' submission that the purpose of the banner image which the survival box was a part of was to highlight the benefit of using Jakavi. The Panel further noted Novartis' submission that there was no comparison being made on the banner, nor was one suggested and Novartis discussed the survival outcome data at a later stage below on the webpage. Whilst the Panel noted that when discussed later on the webpage the survival data was in relation to improved survival benefit compared with BAT (best available therapy), it did not consider that including the 'survival' box in the context of the 'Response', 'Control', 'Survival' graphic was a hanging comparison as alleged and based on the very narrow allegation, the Panel ruled **no breach of Clause 6.1**.

In relation to the substantiation of a survival benefit, the Panel noted Novartis referred to the results of both COMFORT-I and COMFORT-II; COMFORT-I compared Jakavi with placebo and COMFORT-II compared Jakavi with best available therapy. The Panel noted Novartis' submission that in COMFORT-I, there was a 31% reduction in the risk of death in the ruxolitinib arm as compared to placebo (HR 0.69; 95% CI 0.50-0.96; p=0.025); COMFORT-II demonstrated there was a 33% reduction in risk of death in the ruxolitinib arm compared to the BAT arm (HR 0.67; 95% CI 0.44-1.02; p=0.062). Whilst in the Panel's view there was a difference between showing improved survival versus another treatment and improved survival versus placebo, the Panel noted there was nonetheless evidence to show a survival benefit for Jakavi compared with placebo which was statistically significant. In this regard, based on the complainant's narrow allegation, the Panel ruled **no breach of Clause 6.2**.

The Panel noted its comments, and no breach rulings above and consequently ruled **no breach of Clauses 5.1 and 2**.

The Panel noted the complainant's allegation that it was concerning that the claim 'Improved survival benefit compared with BAT' had been put forward without any note about the p value score when the significance had failed.

The Panel noted Novartis' submission that the survival benefit box could be substantiated by the references provided including COMFORT-I and COMFORT-II and was supported by a footnote. The Panel considered that only COMFORT-II was relevant in relation to the claim at issue. The Panel noted Novartis' submission that the nature of the study (a crossover study) had an impact on the p value, however, the data clearly indicated an improved survival benefit compared to BAT as indicated in the SPC and the supporting references on the webpage. The Panel noted that the footnote linked to the claim appeared in smaller font below the heading 'Footnotes and references' and stated 'Estimated 5-year survival in COMFORT-II:56% JAKAVI vs 44% BAT (crossover corrected), HR=0.44, 95% CI (0.18-1.04), P=0.06 (not significant, for descriptive purposes only). The Panel considered the immediate and overall impression of the claim. The Panel considered the claim 'Improved survival benefit compared with BAT' would likely imply to a busy health professional that Jakavi had shown a statistically significant benefit in relation to survival compared with BAT, which was not so and was thus misleading; in the Panel's view, the footnote in smaller font beneath the 'Footnotes & references' heading did not negate this misleading impression and the Panel therefore ruled a **breach of Clause 6.1**. The

supplementary information to Clause 6.1 stated that claims must be capable of standing alone and that, in general, they should not be qualified by the use of footnotes and the like. The Panel noting the results of COMFORT-II, considered that the misleading impression could not be substantiated, and a **breach of Clause 6.2** was ruled.

The Panel considered that Novartis had failed to maintain high standards in this regard and a **breach of Clause 5.1** was ruled. Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted its ruling of Clause 5.1 above, which it considered adequately covered the matter, and **no breach of Clause 2** was ruled.

The Panel noted Novartis' submission that the 'Safety Profile' box did not state Jakavi was a 'safe medication' and that 'well characterised' meant that the characteristics of the safety profile were well known as stated in section 4.8 of the SPC. The Panel noted that the complainant had not provided any evidence to demonstrate that 'well characterised' gave the impression that Novartis had stated Jakavi was 'safe' as alleged and therefore based on this very narrow allegation, the Panel ruled **no breach of Clause 6.1** and subsequently **no breach of Clauses 6.2, 5.1 and 2.**

Complaint received **4 July 2022**

Case completed **29 September 2023**