CASE AUTH/3128/12/18

COMPLAINANT v JANSSEN

Promotion of Imbruvica

An individual complained about a leaflet promoting Imbruvica (ibrutinib) on Janssen-Cilag's exhibition stand at a meeting held in Glasgow in November 2018. The complainant alleged that the leaflet was misleading because it used the claim 'Destination survival' without any mention of survival data and it misleadingly implied that there was a survival benefit with Imbruvica which was not so.

Imbruvica was used in the treatment of chronic lymphocytic leukemia (CLL), relapsed or refractory mantle cell lymphoma (MCL) and Waldenström's macroglobulinaemia (WM).

The detailed response from Janssen is given below.

The Panel noted that the leaflet contained Imbruvica's logo with the strapline (claim) 'Destination survival' on multiple pages. The leaflet was titled, 'Getting started with once-daily, oral, single-agent Imbruvica (ibrutinib)'. The second page of the leaflet listed all of Imbruvica's indications and so, in the Panel's view, the leaflet and therefore the strapline 'Destination survival' might be considered in the context of all Imbruvica's indications.

The Panel considered that health professionals working in oncology would, on the balance of probabilities, associate the strapline 'Destination survival' with overall survival benefit.

The Panel noted Janssen's submission that data supporting ibrutinib's efficacy in improving overall survival in CLL was included in Section 5.1 of the SPC and published by Burger *et al* (2015) and Byrd *et al* (2014). Burger *et al* reported that ibrutinib resulted in significantly longer progression-free survival (primary endpoint) and significantly prolonged overall survival (secondary endpoint) vs chlorambucil in previously untreated CLL patients. Byrd *et al* stated that ibrutinib significantly improved progression-free survival (primary endpoint) and significantly improved overall survival (secondary endpoint) vs ofatumumab in previously treated CLL patients.

The Panel considered the body of clinical data provided by Janssen. The Panel noted that not all studies across all Imbruvica's licensed indications had demonstrated a statistically significant overall survival benefit vs the comparator arm. The Panel considered that as not all of Imbruvica's licensed indications had the body of evidence to support the claim 'Destination survival' which appeared as part of the Imbruvica logo and was included in the leaflet which featured all of Imbruvica's indications, the claim was misleading and incapable of substantiation and breaches of the Code were ruled. The Panel considered that Janssen had failed to maintain high standards in this regard and a further breach of the Code was ruled.

The Panel noted the complainant's allegation that the term 'Destination survival' in the leaflet was misleading in the absence of any survival data within the leaflet. The Panel noted Janssen's submission that the leaflet was intended as a user-friendly simplification of the prescribing information and contained no efficacy data. The Panel did not consider that the claim in question was misleading by virtue of the leaflet not containing survival data as alleged and, in that regard, it ruled no breach of the Code.

An individual complained about information on Janssen-Cilag Limited's exhibition stand which promoted Imbruvica (ibrutinib) at a UK Oncology Nurses Society meeting in Glasgow in November 2018. Imbruvica was used in the treatment of chronic lymphocytic leukemia (CLL), relapsed or refractory Mantle cell lymphoma (MCL) and Waldenström's macroglobulinaemia (WM).

COMPLAINT

The complainant noted that a leaflet (ref PHGB/IBR/0616/0007(9)) on the Janssen stand stated 'Destination survival' (photographs provided). The leaflet did not mention survival, it only referred to: How to give the medicine; side-effects and their management; special populations; precautions for use and prescribing information.

The complainant alleged that the reason there was no mention in the leaflet of 'survival' was because there was no OS (overall survival) benefit with the medicine. Another leaflet stated PFS (progression free survival) benefit not OS benefit (there was no OS benefit with the medicine).

The complainant alleged it was misleading on Janssen's part to use the term 'Destination survival' without any mention of 'survival' data in the first leaflet and secondly, more importantly, as there was no OS benefit – this misled the reader of the first leaflet to think that there was a survival benefit with the medicine when there was none.

In writing to Janssen, attention was drawn to the requirements of Clauses 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Janssen refuted the complainant's remarks that there was no OS benefit with the medicine and that the strapline 'Destination survival' was misleading. Janssen submitted that the leaflet was of a high standard (Clause 9.1) and met the requirements of Clauses 7.2 and 7.4.

Janssen submitted that the strapline 'Destination survival' accompanied the Imbruvica logo and referred to the strength of the efficacy data that

supported the pivotal registrational studies which demonstrated clinically significant survival outcomes. The data supporting ibrutinib's efficacy in improving overall survival (OS) in CLL was listed in Section 5.1 of the Imbruvica summary of product characteristics (SPC) for both patients with untreated CLL (first line therapy) as well as patients who had received at least one prior therapy (relapsed/ refractory patients) as detailed below.

For patients with untreated CLL, Janssen submitted that the marketing authorization application for ibrutinib was supported by a randomised, multi-centre, open-label phase 3 study (PCYC-1115-CA) in patients with treatment naïve CLL who were 65 years and older (n=269). Patients were required to have at least one co-morbidity that precluded the use of front-line chemo-immunotherapy with fludarabine, cyclophosphamide and rituximab. In this study, progression free survival (PFS), as assessed according to International Workshop on CLL (IWCLL) criteria, indicated an 84% statistically significant reduction in the risk of death or progression in the ibrutinib arm. Efficacy results for Study PCYC-1115-CA (Burger *et al*, 2014) were shown in Table 4 and the Kaplan-Meier curves for PFS and OS were shown in Figures 2 and 3, respectively of the SPC that demonstrated a survival benefit for patients treated with ibrutinib. Burger *et al* (2015) concluded that 'Ibrutinib was superior to chlorambucil in previously untreated patients with CLL or small lymphocytic lymphoma, as assessed by progression-free survival, overall survival, response rate, and improvement in hematologic variables'.

For patients with CLL who received at least one prior therapy, Jansen submitted that the marketing authorization for this patient cohort was supported by one uncontrolled study and one randomised, controlled study. The randomised multi-centre, open-label phase 3 study of ibrutinib vs ofatumumab (PCYC-1112-CA) was conducted in patients with relapsed or refractory CLL (n=391). Patients were randomised 1:1 to receive either ibrutinib until disease progression (or unacceptable toxicity) or ofatumumab. Fifty-seven patients randomised to ofatumumab crossed over following progression to receive ibrutinib. The median age of CLL patient was 67 years and the median time since diagnosis was 91 months. Progression free survival as assessed according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the ibrutinib arm. Analysis of OS demonstrated a 57% statistically significant reduction in the risk of death for patients in the ibrutinib arm. The authors of this pivotal study concluded that ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or small lymphocytic lymphoma (SLL) (Byrd *et al*, 2014).

Janssen submitted that the intent of the leaflet ('Getting started with once-daily, oral, single-agent' (ref PHGB/IBR/0616/0007(9)), specifically to guide UK health professionals commencing treatment in new patients, was to highlight the safety and appropriate use of ibrutinib:

- The NICE (National Institute for Health and Care Excellence) Technical Appraisal Guidance for ibrutinib use in CLL patients and guidance on which patients were eligible to receive ibrutinib
- How to administer ibrutinib – dosing adjustments, caution in special populations and drawing attention to potential drug interactions and precaution for use.

The guide was intended as a user-friendly simplification of the prescribing information to educate health professionals, and in particular, oncology nurses and pharmacists by guiding patients on the use of ibrutinib to treat their disease. Whilst each section page of the guide was introduced in the left-hand bottom corner with the strapline 'Destination Survival', at no point was any efficacy information or, specifically to this case, survival data listed within this guide and as such, capable of substantiation. The guide was referenced by the SPC that would contain all the distinct information for ibrutinib.

Janssen submitted that the complainant's assertation that 'there is no OS benefit' was incorrect as the pivotal studies outlined above demonstrated a survival benefit (PFS and OS). Janssen therefore submitted that the materials had maintained high standards (Clause 9.1) and that the strapline 'Destination survival' was accurate, balanced, fair and unambiguous (Clause 7.2) and capable of substantiation (Clause 7.4).

Janssen stated that the intent of the leaflet was to ensure therapy management of CLL for patients considered for ibrutinib and to inform prescribers about specific precautions as outlined in the prescribing information. Janssen refuted the complainant's suggestion that the guide had no survival data as the Code allowed for claims to be made about a product provided they could be substantiated. Janssen was confident that the efficacy data provided within the SPC Section 5.1 clearly substantiated the claim. Janssen therefore submitted that the strapline 'Destination survival' was accurate, balanced and objective and the materials used at the meeting were within the spirit and guidance of the Code.

Following a request for further information, Janssen provided additional survival data for further Imbruvica indications.

Janssen submitted that the safety and efficacy of Imbruvica in patients previously treated for CLL were further evaluated in a randomised, multicentre, double-blinded phase 3 study of Imbruvica in combination with bendamustine/rituximab (BR) vs placebo + BR (Study CLL3001-HELIOS STUDY). Patients (n=578) were randomised 1:1 to receive either Imbruvica 420mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. Progression free survival (PFS) was assessed according to IWCLL criteria. Efficacy results for Study CLL3001 were shown in the SPC (details provided). The HELIOS study was conducted in patients with relapsed/refractory CLL/ SLL and was the first trial to show a survival benefit with ibrutinib-based therapy vs a standard chemo-immunotherapy regimen, even in the context of

a crossover design. These results supported the continued use of ibrutinib, with maintenance of superior PFS and OS vs the placebo + BR arm and an increase in overall response rate and complete response rates over time. It was notable that longer-term follow-up revealed a significant improvement in survival for ibrutinib + BR-treated patients compared with placebo + BR, despite the possibility of crossover after progression.

For treatment of adults with relapsed or refractory mantle cell lymphoma (MCL), Janssen submitted that study PCYC-1104-CA was a multicentre, open-label phase 2 registration trial of ibrutinib (n=111) where the primary endpoint was the rate of overall response and secondary endpoints included survival efficacy outcomes such as PFS, OS and safety. The 24-month PFS and OS rates were 31% (95% confidence interval [CI], 22.3-40.4) and 47% (95% CI, 37.1-56.9), respectively. At a median follow up of 26.7 months, the median PFS was 13 months (95% CI: 7.0, 17.5 and the median OS was 22.5 months (95% CI: 13.7, not estimable). In study MCL3001 (RAY), Janssen submitted that median PFS survival was significantly improved in the ibrutinib group compared with the temsirolimus group (95% CI); Ibrutinib 14.6 months (10.4, not estimable) vs temsirolimus 6.2 months (4.2, 7.9) [HR = 0.43 [95% CI: 0.32, 0.58]]. After a median follow up for over three years, ibrutinib significantly prolonged median PFS vs temsirolimus (15.5 vs 6.2 months; p < 0.0001). Median OS was not reached for ibrutinib vs 21.3 months for temsirolimus (HR, 0.76 [95% CI, 0.53-1.09]; p = 0.1324). The difference was not statistically significant; however, it should be noted that 32 (23%) of temsirolimus patients (23%) crossed over to ibrutinib. 1-year survival rates were 68% for ibrutinib and 61% for temsirolimus. After a median follow up of over 3 years, median OS was nearly 7 months longer with ibrutinib vs temsirolimus (30.3 vs 23.5 months; HR = 0.74 [0.54-1.02]; p = 0.0621). Further in a pooled analysis 3.5 year follow up across studies 1104, SPARKLE and RAY, Janssen submitted that Rule *et al* (2019) demonstrated overall, median PFS and OS were 12.5 (95%CI: 9.8-16.6) and 26.7 (95%CI: 22.5-38.4) months, respectively. Patients receiving ibrutinib in second line had better outcomes than those treated in later lines (>1 prior line): median PFS and OS were 25.4 months (95%CI: 17.5- 57.5) and not reached [NR; 95%CI: 36.0-not estimable)], respectively.

For treatment of adults with Waldenström's in one prior therapy or first line treatment for patients unsuitable for chemo-immunotherapy, Janssen submitted that study NCT01614821 was a prospective open-label, multicentre, single-arm phase 2 study (n=63) where the primary endpoint was the rate of overall response and secondary endpoints included survival efficacy outcomes such as PFS, OS and safety. At 24 months, the estimated rate of PFS was 69.1% (95% CI, 53.2-80.5) and the estimated rate of OS was 95.2% (95% CI, 86.0-98.4). Ibrutinib had an overall response of 91% which had demonstrated single active agent for relapsed or refractory Waldenström's macroglobulinaemia (WM) where European Medicines Agency (EMA) approval was attained. Janssen further submitted that iNNOVATE was an ongoing, randomised phase III, placebo-controlled study where a subset analysis was performed from the non-randomised, single-arm group of patient's refractory to rituximab who were treated with ibrutinib (n=31). At a median follow-up of 18·1 months (17·5 – 18·9), the proportion of patients with an overall response was 28 [90%] of 31 (22 [71%] of patients had a major response), the estimated 18-month PFS rate was 86% (95% CI 66–94), and the estimated 18 month OS rate was 97% (95% CI 79–100). This study population differed in a clinically significant way from NCT01614821 with respect to higher median lines of previous regimens and its focus on patient's refractory to the most recent rituximab containing regiment.

With respect to the procedural handling of this complaint, Janssen noted that the exact words of the complainant were, 'There is no OS benefit with the drug'. Janssen submitted that this was mentioned three times in the complaint and was in itself an all-embracing complaint, which was misleading, not capable of substantiation and factually incorrect. Janssen submitted that it had demonstrated and documented survival data for its licensed indications with data described above and within Section 5.1 of the Imbruvica SPC.

Janssen noted that Paragraph 2.2 of the Constitution and Procedure stated 'Rulings are made on the basis that a complainant has the burden of proving their complaint on the balance of probabilities'. Janssen submitted that the complainant had not achieved this as he/she alleged no survival data across Imbruvica's indications when survival data had been demonstrated across its indications as noted above and within the SPC.

PANEL RULING

The Panel noted Janssen's submission that 'Destination survival' was a strapline that accompanied the Imbruvica logo. The Panel considered that this strapline was a claim for Imbruvica. Clause 7.2 required claims to be, *inter alia*, accurate, balanced, fair, objective and unambiguous. Clause 7.4 stated that claims must be capable of substantiation.

The Panel noted that the 'Getting started' leaflet contained Imbruvica's logo with the strapline 'Destination survival' on multiple pages alongside images depicting space travel. The leaflet was entitled, 'Getting started with once-daily, oral, single-agent Imbruvica (ibrutinib)'. The second page of the leaflet listed all of Imbruvica's indications. The third and fourth pages of the leaflet referred to both CLL and MCL [mantle cell lymphoma] dosage instructions. In the Panel's view, the leaflet was not solely about CLL and therefore the strapline 'Destination survival' might be considered in the context of all Imbruvica's indications.

The Panel considered that health professionals working in oncology would, on the balance of probabilities, associate the strapline 'Destination survival' with overall survival benefit.

The Panel noted Janssen's submission that data supporting ibrutinib's efficacy in improving overall survival in CLL for both patients with untreated CLL as well as patients who had received at least one prior therapy was included in Section 5.1 of the SPC and published by Burger *et al* (2015) and Byrd *et al* (2014), respectively.

The Panel noted that Burger *et al* (2015) was a Phase III trial comparing ibrutinib with chlorambucil in previously untreated CLL. The Panel noted that the study authors stated that ibrutinib resulted in significantly longer progression-free survival (primary endpoint) and significantly prolonged overall survival (secondary endpoint) vs chlorambucil.

The Panel noted that Byrd *et al* (2014) was a Phase III trial comparing ibrutinib with ofatumumab in previously treated CLL. The Panel noted that the study authors stated that ibrutinib significantly improved progression-free survival (primary endpoint) and significantly improved overall survival (secondary endpoint) vs ofatumumab.

The Panel considered the body of clinical data provided by Janssen. The Panel noted that not all studies across all Imbruvica's licensed indications had demonstrated a statistically significant overall survival benefit vs the comparator arm. For example, in the HELIOS study (Chanan-Khan *et al*, 2016), which was a Phase III trial of ibrutinib combined with bendamustine and rituximab compared with placebo (plus bendamustine and rituximab) in previously treated CLL, the authors stated that there was no statistically significant difference in overall survival between the treatment arms. The Panel further noted Janssen's submission that the difference in overall survival between treatment arms in a mantle cell lymphoma study (MCL3001) of ibrutinib vs temsirolimus was not statistically significant. Furthermore, the Panel noted that for the Waldenström's macroglobulinaemia indication, the efficacy of ibrutinib was evaluated in an open-label, single-arm Phase II trial (NCT01614821) and in a non-randomised, single-arm subset analysis of an ongoing Phase III trial (iNNOVATE study).

The Panel noted its comments above. Based on the information before it, the Panel considered that not all of Imbruvica's licensed indications had the body of evidence to support the claim 'Destination survival' which appeared as part of the Imbruvica logo and was included in the leaflet in question which featured all of Imbruvica's indications. The Panel considered, therefore, that the claim was misleading and incapable of substantiation and a breach of Clauses 7.2 and 7.4 was ruled.

The Panel considered that Janssen had failed to maintain high standards in this regard and a breach of Clause 9.1 was ruled.

The Panel noted the complainant's allegation that the term 'Destination survival' in the 'Getting started' leaflet was misleading in the absence of any survival data within the leaflet. The Panel noted Janssen's submission that the leaflet was intended as a user-friendly simplification of the prescribing information and contained no efficacy data. The Panel did not consider that the claim in question was misleading by virtue of the leaflet not containing survival data as alleged and, in that regard, ruled no breach of Clause 7.2.

Complaint received **2 December 2018**

Case completed **12 July 2019**