

**DISPUTE RESOLUTION PANEL OF THE PHARMACEUTICAL PRICE
REGULATION SCHEME**

DECISION DATED 9 FEBRUARY 2016

IN THE MATTER OF

PPRSDRP/FEBRUARY/2016/01

NOVARTIS PHARMACEUTICALS UK LIMITED

-and-

DEPARTMENT OF HEALTH

DECISION OF THE PPRS DISPUTE RESOLUTION PANEL

- 1 This is a decision of the Dispute Resolution Panel (“the Panel”) appointed under the 2009 and 2014 Pharmaceutical Price Regulation Schemes to consider and provide reasoned decisions in respect of disputes arising under the 2014, 2009, 2008 and 2005 Schemes. This dispute arises and is referred to the Panel under the 2014 Scheme. The Panel consists of Patrick Walker (Chairman), Sir Robert Culpin and David Hill.

Issues

- 2 The dispute concerns the classification under the 2014 Scheme of the Novartis branded product Ultibro Breezhaler (“Ultibro”). It is Novartis’ case, disputed by the Department of Health (“the Department”) that Ultibro should not be included in the sales covered by the PPRS Payment under the 2014 Scheme, because it qualifies as a new product within the definition set out in Paragraph 6.10 of the Scheme.
- 3 By paragraph 6.7 of the Scheme, “Sales Covered by the PPRS Payment” expressly excludes “Sales of new products as defined in paragraph 6.10 below.” Under

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Paragraph 6.10 “**For this purpose, new products are defined as follows: products introduced after the 31st December 2013 following the granting of an EU or UK new active substance marketing authorisation from the appropriate licensing body.**” “New active substance marketing authorisation” is not defined in the PPRS, or elsewhere so far as the company and Department know.

- 4 Novartis summarises the product as follows: *“Ultibro is a new fixed dose combination product (indacaterol /glycopyrronium bromide) that was granted a marketing authorisation by the European Commission under the centralised procedure on 19 September 2013. The original Ultibro Marketing Authorisation does not indicate the status of the grant. Both indacaterol and glycopyrronium bromide have previously been available in the EU as constituents of other medicinal products, however the fixed dose combination has not previously been authorised.”*
- 5 It is Novartis’ case that the fixed dose combination of two established substances, where the combination has not previously been marketed, can and in this case does constitute a ‘new active substance’. In the case of Ultibro, *‘the physical properties of the two constituents produce different effects’* when combined, with *‘enhanced clinical benefits,’* so that *‘Ultibro is not simply the sum of the two substances which make it up.... [and] the dosage for Ultibro is different from the combined dosage of the two constituent elements.’* The Department does not dispute the clinical benefits of Ultibro but says that the test for the PPRS is whether ‘the appropriate licensing authority’ has granted a ‘new active substance marketing authorisation’, and that in this case there has been no such grant.
- 6 The parties agree that there is no list of marketing authorisations with new active substance status. They also agree that Ultibro is a new product in the ordinary sense of the words, unique, innovative, and previously unmarketed. There is no dispute that it underwent substantial trials, required sophisticated manufacture and adds

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value to the monotherapies which are combined in it. The product leaflet for Ultibro says that the active substances are indacaterol and glycopyrronium, not the fixed dose combination Ultibro itself.

Arguments

- 7 The Panel has studied an extensive bundle of documents, including detailed reasoned statements of position, and also benefited from clear presentations and discussion at a hearing. The Panel is grateful to both the company and the Department representatives. Among points raised were the following.
- 8 Novartis explained that, to secure its EU marketing authorisation, it had to submit a full, as opposed to an abridged, application under article 10(b) of Directive 2001/83/EC. It did not have to resubmit evidence for indacaterol or glycopyrronium, which were already authorised, but in respect of Ultibro had to conduct and submit the full panoply of pharmaceutical and pre-clinical tests, and clinical trials, quite independently of the previous authorisations for indacaterol and glycopyrronium.
- 9 Novartis said that the application was made under article 3(2)(b) of Regulation no 726/2004, which is for products which constitute “a significant therapeutic, scientific or technical *innovation*,” and not under article 3(2)(a), which is for products which contain “a *new active substance* which, on the date of entry into force of this Regulation, was not authorised in the Community” (Panel italics). Novartis explained that this was the normal convention for all fixed dose combinations, only provided the way into the authorisation process and did not determine the outcome.
- 10 Novartis said the outcome was that a rigorous scientific assessment led to a full stand-alone marketing authorisation with full data exclusivity, entirely independent of indacaterol and glycopyrronium.

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- 11 The key facts in this were unchallenged: full application, the route for the application not determining the outcome, Ultibro fully authorised in its own right. But did this establish that Ultibro was authorised as a new active substance, or simply new? Novartis argued that any fixed dose combination, not previously marketed, constituted a new active substance.
- 12 Novartis suggested that differences in the wording of the 2014 PPRS from its predecessors were significant. The 2014 Scheme says only that the definition of new products excluded from the PPRS Payment “does not include biosimilars or line extensions...” By contrast, the 2005 Scheme, for example, said that “where a product has not been subject to a new active substance marketing authorisation ... this can include new products regarded by a company as innovative but ...not classified...as new active substances; combination products containing active substances that have been marketed separately...” etc. Novartis said that the 2014 Scheme could have said in similar terms that the definition of new products excluded fixed dose combinations; that it was suggestive that it did not do so; and that this may well have reflected the objective of the 2014 PPRS to encourage innovation.
- 13 Both parties agreed that if Ultibro and other fixed dose combinations were to be classed as new active substances and so excluded from the PPRS Payment, the 2014 Scheme required the cost to fall on other products and companies, and not the Department. Novartis said that Ultibro is cheaper than its constituent parts and it did not believe this cost would be large.
- 14 The Department’s main response was that the PPRS definition of new products is strictly limited to ones with “a new active substance marketing authorisation from the appropriate licensing body”. In this case the appropriate body is the EU Commission and its agency the European Medicines Agency (EMA). The Department asked the

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EMA whether Ultibro was authorised as a new active substance and the answer was no.

- 15 What other guidance might be relied on? The Marketing Authority recorded in the Official Journal does not specify whether such authority is in respect of a new active substance. Early correspondence between Novartis and the Department might be construed as consistent with the Department's case but the Panel accepts it merely reflected a routine approach and is not persuasive. Novartis has not challenged any presumption within the EU that combination products are innovative but not new active substances, but in the Panel's view is not required to do so. The Department seeks to rely on answers to questions put to the Medicines and Healthcare Products Regulatory Agency (MHRA) but Novartis challenges whether the right questions were asked.

Conclusions

- 16 Weighing the whole of the evidence, the Panel finds that a number of indicators point consistently in one direction: the company applied for marketing authorisation for Ultibro as an innovative product rather than a new active substance; that is normal for all new fixed dose combinations; the scientific assessment confirmed that it is innovative but did not suggest it is a new active substance; nothing in that assessment or any other evidence the Panel has seen would have led the EU authorities to think they were authorising a new active substance; the EMA does not think it did so; and the patient information for Ultibro says that the active substances are indacaterol and glycopyrrium, not the combination.
- 17 The Panel finds the indicators in the other direction less persuasive: the application process for Ultibro may well have been similar to that for an undisputed new active substance, but that does not make them the same; one could take the view that any new fixed dose combination should be treated as a new active substance, but the

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panel has not seen evidence that either the EU authorities or the parties to the PPRS take that view, or that it accords with normal usage; the wording of the 2014 PPRS differs from its predecessors, but the words which are different are not in the definition of new products; and if the parties to the PPRS had wanted to extend that definition to new fixed dose combinations, they could have done so.

- 18 The Panel considers that the evidence overall is consistent with Ultibro's being an innovative product but not a new active substance. The Panel has not seen evidence that the licensing authorities in the EU took a different view, or that the marketing authorisation they granted Novartis was a 'new active substance marketing authorisation'.
- 19 In these circumstances, the Panel concludes that the Department was right to treat Ultibro sales as Sales Covered by PPRS Payment.

PANEL MEMBERS

Patrick Walker (Chairman)

Sir Robert Culpin

David Hill