CASE AUTH/3751/3/23

EX-EMPLOYEE v OTSUKA

Jinarc training website

CASE SUMMARY

This case was in relation to instructions on the Jinarc training website, and the omission of information in one of the documents on the website, the Healthcare Professionals Educational Guide, which formed part of the additional Risk Minimisation Measures for Jinarc.

The Panel ruled a breach of the following Clause of the 2021 Code in relation to the Jinarc training website:

Breach of Clause 6.1	**Providing misleading information**

The Panel ruled a breach of the following Clauses of the 2021 Code in relation to the Healthcare Professionals Educational Guide:

Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1	**Providing misleading information**
Breach of Clause 2	**Bringing discredit upon, and reducing 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 a complainant who described themselves as an ex-employee about Otsuka Pharmaceuticals UK Limited. The complainant could not be contacted on the details provided.

COMPLAINT

The complaint wording is reproduced below:

> "I am writing about [the] Otsuka website – [website link]. Main page of [the] website says - Healthcare professionals must also register their details once they have read and understood the educational materials allowing them to become certified prescribers

eligible to prescribe Jinarc. Therefore, any HCP [healthcare professional] wishing to prescribe Jinarc must complete the following: Step 1: Completion of training materials Step 2*: Completion of enrolment form *Please note that while step 2 is not a mandatory requirement to prescribe the product it will enable Otsuka to send annual reminders to trainees to update their training on the RMP [risk minimisation plan] materials as per MHRA [Medicines and Healthcare products Regulatory Agency] requirements. This is confusing. Otsuka is trying to get prescribers details by saying they must give them but lower down then saying [it is] not mandatory. One of the document[s] on [the] website - HCP educational guide UK-JIN-2100005 October 2021 - says - 'What are the special warnings and precautions for use?

- Idiosyncratic hepatic toxicity (see page opposite)
- Access to water
- Dehydration
- Urinary outflow obstruction
- Fluid and electrolyte balance
- Serum sodium abnormalities
- Anaphylaxis
- Lactose intolerance
- Diabetes mellitus
- Uric acid increases
- Effect of Jinarc on glomerular filtration rate (GFR)'.

SmPC [Summary of Product Characteristics] lists one more that has not been included – 'Chronic Kidney Disease [CKD]. Limited safety and efficacy data are available for Jinarc in patients with CKD late stage 4 (eGFR< 25 mL/min/1.73 m^2). There are no data in patients with CKD stage 5. Tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5'.

Why has this not been included? Think of the harm that could become patients."

When writing to Otsuka UK, the Authority asked it to consider the requirements of Clauses 2, 5.1 and 6.1 of the 2021 Code.

OTSUKA'S RESPONSE

The response from Otsuka UK is reproduced below:

"**Background**

Jinarc (tolvaptan) is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease. Marketing Authorisation [MA] was granted by the EMA [European Medicines Agency] in 2015 (and by Great Britain after Brexit on 01/01/2021). From the initial Marketing Authorisation in 2015 it has been the subject of a Risk Minimisation Plan and has required additional Risk Minimisation Measures (aRMM) to ensure that Jinarc is used as safely as possible. Three specific areas that to date require aRMM are the 'Liver Injury in ADPKD Patients', 'Volume Depletion, Dehydration and Associated Sequelae such as Renal Dysfunction' and the 'Pregnancy outcome data'. The aRMM for these are composed of Healthcare Professional education guide, Jinarc

Prescribing Checklist, Patient Education Brochure for all three and Patient Alert Card for the liver injury and volume depletion. Otsuka has worked with the MHRA in the creation of these materials. The detailed information on the RMP and aRMM is enclosed (MHRA follows the EMA guidance on the RMPs).

The material in question is accessible from the training website at issue in this case [website link] as well as from the eMC website [website link], where it appears together with the rest of the aRMM materials under the heading: Risk Materials. At present the only proactive signposting to this material by Otsuka Pharmaceuticals UK Ltd (OPUK) is through yearly reminders sent out by the Otsuka pharmacovigilance (PV) team requesting registered HCPs to complete the refresher training. OPUK no longer has any promotional activities relating to Jinarc, including representative activities. Consequently, there are no briefing documents for the website or item. Healthcare professionals can also ask for hard copies of the materials which are sent out on request.

In order to enter the website, the individuals would need to self-certify as a[n] HCP, which would give them access to the four aRMM materials mentioned above. If an individual self certifies as a non-HCP, they are taken into another page which contains links to reference information and the OPUK company website.

From our understanding, the complainant raises two main concerns, as noted below:

1. The Jinarc training website is confusing in relation to the requirement for the HCP to provide their details.
2. HCP educational guide does not include one of the special warnings and precautions listed in the SmPC.

We will address each of these areas separately.

The Jinarc training website is confusing in relation to the requirement for the HCP to provide their details

In the UK Jinarc was also under a controlled distribution agreement mandated by the MHRA, which meant that in order for a centre to be able to order Jinarc from the distributors, the prescribing HCP needed to complete aRMM training and provide their details to be maintained on a tracker. This was provided and managed through the training website [website link] developed by OPUK specifically for this purpose. The information provided is only accessible by the PV department of Otsuka and is not made available to the commercial part of the organisation.

In 2020 the MHRA undertook a review and informed OPUK that the controlled distribution model for Jinarc was no longer required as prescribers were experts in the management of ADPKD, worked in the highly specialised centres, the performance of liver monitoring had become a standard practice and that the approved educational programme, comprising aRMM materials, was considered sufficient to mitigate the risks. Although the controlled distribution model was no longer required, the MHRA requested that we should ensure that the training website continued to be active, and that Otsuka carried on with maintaining a tracker of individuals completing the training for audit trail and in order to notify them about refresher training or offer hard copies of the materials.

To follow the instruction from the MHRA, the training website was updated with the information under the asterix [asterisk] provided by the complainant, which informed the HCPs that step 2 is no longer mandatory, however they will receive annual reminders about the RMP training should they enrol.

We acknowledge that the instructions on the website could have been made clearer in this regard and will update the wording to ensure there is no confusion as to whether the provision of HCP details is mandatory. Otsuka therefore accepts a breach of Clause 6.1 of the 2021 Code regarding these instructions on the website being ambiguous. Our understanding was that the complainant had concerns that OPUK were collecting this information unnecessarily and wanted to confirm as noted above that the information provided by the HCPs is only accessible by the PV department of Otsuka and is not made available to the commercial part of the organisation. The provision of this information would allow OPUK to ensure that the updated information relating to this RMP could be sent to the respective HCPs who had requested to be kept updated and was only used for this purpose in accordance with MHRA requirements.

HCP educational guide does not include one of the special warnings and precautions listed in the SmPC.

ADPKD [autosomal dominant polycystic kidney disease] is a chronic, progressive condition characterized by the development and growth of cysts in the kidneys and other organs. In the majority of patients eventually there is a deterioration in renal function and progression to end stage renal disease thus patients with ADPKD are under the care of specialist nephrologists from the time of diagnosis for monitoring of renal function and appropriate reno-protective pharmacotherapy. As Jinarc is indicated only in the patients with stage 1 to 4 CKD and evidence of rapidly progressing disease, the prescription and the monitoring of renal function is done by nephrologists experienced in the management of patients with CKD and capable of making an appropriate therapeutic decision for different stages of the disease.

As stated above, the initial development of the aRMM materials has been done by OPUK with the review and approval by MHRA when the molecule received the initial MA in 2015. Further, the content of all the aRMM materials undergoes review and approval by regulatory authorities every time any of the content changes prior to being released by the company to HCPs and/or patients/carers. Patient safety is paramount in the MHRA review of the materials related to RMP.

The point that is being raised by the complainant has received detailed attention in the last review of the Jinarc aRMM materials in 2021. A person in the PromoMats review cycle commented on the absence of the information on Special precaution for use in Chronic Kidney Disease in the section ‘What are the special warnings and precautions for use?’ in the HCP education guide and requested that this precaution was added.

A consensus meeting took place involving [three senior employees], [a] compliance contractor as well as the person who raised the query to agree if this specific precaution should be added to the HCP education[al] guide. A consensus was reached that the CKD special precaution did not need to be included for the following key reasons.

- These RMP material[s] in question had already been approved by the MHRA in their current form in November 2021
- The purpose of the materials was not to replicate the entirety of sections of the SmPC verbatim. Instead, as a suite of resources, they serve to highlight to prescribers, patients and others, key points and direct the reader to other sources (such as the SmPC) as appropriate

We would like to reinforce the purpose of the HCP educational guide, which is to is [sic] educate the clinicians managing patients with Jinarc (who are renal specialists) about the increased risk of hepatotoxicity, risk of dehydration and the need for pregnancy prevention due to potential risk of reproductive toxicity related to the drug. While all the information on special warnings and precautions for use in the SmPC is important, the purpose of the educational guide is to provide details of very specific risks mentioned above.

A clear statement "Please see Section 4.4 of the Jinarc SmPC for full details." appears at the bottom of the section titled 'What are the special warnings and precautions for use?' which is queried by the complainant. HCPs are directed to consult the SmPC a total of seven times, reinforcing that this document is not meant to be exhaustive or a replication in full of the SmPC.

With the above in mind, OPUK strongly refutes that patient safety was compromised and denies any breach of Clauses 6.1, 5.1 and 2 of the 2021 Code."

PANEL RULING

The Panel noted that the complaint was in relation to instructions on the Jinarc (tolvaptan) training website and the omission of information in one of the documents on the website, Healthcare Professionals Educational Guide, which formed part of the additional Risk Minimisation Measures (aRMM) for Jinarc.

Instruction on Jinarc training website

The Panel noted that the webpage at issue, beneath a header containing the Jinarc logo and the heading 'Training Portal', stated:

"Welcome to the JINARC® (tolvaptan) training website for healthcare professionals (HCPs) in the UK. The Medicines and Healthcare Products Regulatory Agency (MHRA) requires Otsuka UK to ensure healthcare professionals who prescribe Jinarc have access to educational materials that provide important information regarding the appropriate use of the drug. Healthcare professionals must also register their details once they have read and understood the educational materials allowing them to become certified prescribers eligible to prescribe Jinarc. Therefore, any HCP wishing to prescribe Jinarc must complete the following:

- Step 1: Completion of training materials
- Step 2*: Completion of enrolment form."

The asterisk at Step 2 led to a footnote, in smaller typeface, immediately beneath the aforementioned text, which stated, "Please note that while step 2 is not a mandatory

requirement to prescribe the product it will enable Otsuka to send annual reminders to trainees to update their training on the RMP materials as per MHRA requirements". This text was followed by the statement "It is recommended that the materials on this site are used in conjunction with the full Summary of Product Characteristics".

Adjacent to the above body of text appeared two prominent red tabs which read 'Step 1 | Training materials' and 'Step 2 | Enrolment'. An expanded version of the first tab Step 1 | Training materials, included four large tiles called 'HCP Educational Guide', 'HCP Prescribing Checklist Electronic', 'Patient Alert Card' and 'Patient Carer Education Brochure'. The expanded version of the second tab Step 2 | Enrolment stated, 'If you have reviewed the training slides above, please complete the enrolment form to become a JINARC® prescriber by clicking the link below'.

The Panel noted the complainant's allegation that the 'main' page of the Jinarc training website was confusing with regard to the requirement for health professionals to provide their details.

The Panel noted Otsuka's submission that Jinarc had been under a controlled distribution agreement mandated by the MHRA, which meant that for a centre to be able to order Jinarc from the distributors, the prescribing health professional needed to complete aRMM training and provide their details to be maintained on a tracker; this was provided and managed through the training website developed by Otsuka UK specifically for this purpose.

The Panel noted that an MHRA letter to Otsuka dated 14 April 2020 stated, among other things:

> "Taking expert advice into account, the MHRA would like to inform you that the existing controlled distribution model for Jinarc is no longer required."

A further letter from the MHRA dated 28 April 2020 stated, among other things:

> "In order to provide an audit trail for training you are requested to track who has undergone training and use this information to offer refresher training or hard copies of the materials periodically, for example at least annually."

It appeared to the Panel that the MHRA had requested Otsuka to continue collecting health professional details on the designated training portal in order to offer, among other things, periodic refresher training, however, health professionals' details did not need to be maintained on a register to enable them to prescribe Jinarc.

The Panel considered that the text on the training webpage at issue was contradictory and therefore misleading. It first stated that health professionals must register their details to become "certified prescribers eligible to prescribe Jinarc", followed by a footnote to the contrary which stated that completion of the enrolment form was "not a mandatory requirement to prescribe the product", however, further down the webpage it again stated, "please complete the enrolment form to become a JINARC® prescriber". In the Panel's view, this misleading impression was not dispelled by the text on the enrolment form which referred to 'a register of prescribers' who had completed the training being maintained 'as agreed with the Medicines and Healthcare Products Regulatory Agency'.

In the Panel's view, the instructions to health professionals on the introductory webpage of the Jinarc Training Portal in relation to the need for and purpose of collecting their details was ambiguous, and **a breach of Clause 6.1** was ruled, as accepted by Otsuka.

Healthcare Professionals Educational Guide

The Panel noted the complainant's allegation that the healthcare professionals educational guide did not include the special warnings and precautions for use in relation to chronic kidney disease (CKD) from the Jinarc SPC.

The Panel noted that the Jinarc SPC, Section 4.4, Special warnings and precautions for use, Chronic Kidney Disease, stated "*Limited safety and efficacy data are available for Jinarc in patients with CKD late stage 4 (eGFR< 25 mL/min/1.73m^2). There are no data in patients with CKD stage 5. Tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5*".

This information was also referred to in Section 4.2, Posology and method of administration, under 'Dose Titration' where it stated, "*The safety and efficacy of Jinarc in CKD stage 5 have not been explored and therefore tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5 (see section 4.4)*" and under Special Populations, Renal Impairment, which stated "*Limited data are available for patients with CKD late stage 4 (eGFR < 25 mL/min/1.73m^2). No data are available for patients with CKD stage 5. Tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5 (see section 4.4)".*

The Panel noted that the healthcare professionals educational guide, in the section titled 'What is the purpose of this guide?' stated, among other things:

> "This document summarises important information on the potential risk of hepatic toxicity and provides guidance on how to manage this risk. In addition, it provides important information about pregnancy prevention before and during the treatment with Jinarc.
>
> This guide will enable you to:
>
> - Understand what Jinarc is indicated for and how it should be used
> - **Be aware of warnings and precautions for use** [emphasis added by the Panel], (in particular idiosyncratic hepatic toxicity and the risk of dehydration and how it can be prevented, identified and managed)
> - Provide important safety information to your patients
> - Be aware of documents available that provide information on Jinarc and their purpose
> - Be aware of the mechanism to report adverse events
>
> This document does not replace the Summary of Product Characteristics (SmPC), which should be read thoroughly before prescribing or dispensing Jinarc. The patient should also be advised to read the Patient Information Leaflet (PIL). The SmPC and PIL for Jinarc can be found at www.medicines.org.uk/emc/."

The Panel noted that the section of the guide titled 'What are the special warnings and precautions for use?' listed the following:

- Idiosyncratic hepatic toxicity
- Access to water
- Dehydration
- Urinary outflow obstruction
- Fluid and electrolyte balance
- Serum sodium abnormalities
- Anaphylaxis
- Lactose intolerance
- Diabetes mellitus
- Uric acid increases
- Effect of Jinarc on glomerular filtration rate (GFR).

Beneath this list it stated, "Please see Section 4.4 of the Jinarc SmPC for full details".

The Panel noted that this section of the educational guide did not refer to the special warning or precaution for use in relation to CKD, as stated in the Jinarc SPC. The Panel further noted that the omitted information did not appear anywhere in the eleven-page educational guide.

The Panel noted that Jinarc was indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 **at initiation** of treatment **with evidence of rapidly progressing disease** and therefore considered that the special warning and precaution '*Limited safety and efficacy data are available for Jinarc in patients with CKD late stage 4 (eGFR< 25 mL/min/1.73m^2). There are no data in patients with CKD stage 5. Tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5'* was relevant to the educational guide.

The Panel did not accept Otsuka's inference that the guide was solely to provide details of the 'very specific risks' related to increased risk of hepatotoxicity, risk of dehydration and the need for pregnancy prevention. Whilst such matters were emphasised in the guide it was clear that the guide went beyond these matters. The section 'What is the purpose of this guide', reproduced above, was broad and featured a list of 5 matters including 'understand what Jinarc is indicated for and how it should be used' and to 'be aware of warnings and precautions for use (in particular idiosyncratic hepatic toxicity and the risk of dehydration and how it can be prevented, identified and managed)'.

The Panel considered that listing all but one special warning and precaution for use in the section titled 'What are the special warnings and precautions for use?' was misleading. The section title implied that the list was complete and contained all special warnings and precautions and that was not so. The text beneath the list 'Please see Section 4.4 of the Jinarc SmPC for full details' was insufficient to negate the misleading impression. While it might be clear that additional details on each special warning and precaution listed in the guide would be available in the SPC, the Panel considered that it was not clear that the list was incomplete. The Panel considered that the omission of reference to treatment discontinuation if renal insufficiency progresses to CKD stage 5 was misleading, and the Panel ruled **a breach of Clause 6.1**.

The Panel noted Otsuka's submission that a reviewer of the material at issue, in the company's electronic approval system, had commented on the absence of the information on special precautions for use in CKD and requested that this precaution was added.

The Panel further noted Otsuka's submission that a consensus meeting took place involving senior medical employees and, according to Otsuka, a consensus was reached that the CKD special precaution did not need to be included for two 'key' reasons, one of which was that the material in question had already been approved by the MHRA in its current form.

The Panel was concerned that the issue had been identified and raised internally within Otsuka but that an amendment was not made for reasons including that the MHRA had already approved the material. The Panel considered that the company had failed to identify the seriousness of the issue raised and appeared to deflect its responsibilities under the Code in this regard by referring to prior approval by the MHRA. The Panel considered that Otsuka had failed to maintain high standards in this regard and ruled **a breach of Clause 5.1**.

The Panel noted that whilst the SPC for Jinarc stated that tolvaptan treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements, the educational guide had a circulation beyond such physicians. Its certificate and meta data showed that it was available in digital and printed form, could be distributed by Key Account Managers, and that its target audience included pharmacists or nurses treating ADPKD patients.

Clause 2 was a sign of particular censure and was reserved for such use. Prejudicing patient safety was an example of an activity likely to lead to a breach of this clause. The Panel bore in mind that Jinarc was a black triangle medicine subject to additional risk minimisation measures. Companies needed to take the utmost care when producing materials to ensure that readers could not be misled as to the safety profile of the medicine. The educational guide was also available as hard copy material and was intended to be a resource that health professionals would regularly familiarise themselves with. It was crucial that health professionals and others could rely completely upon the industry for accurate and up-to-date information about their medicines, including special warnings and precautions for use, the omission of which could potentially impact patient safety. The Panel considered that the misleading impression given that the educational guide contained reference to all of the special warnings and precautions for use, which was not so, as it omitted important information related to treatment discontinuation if renal insufficiency progresses to CKD stage 5, meant, on balance, that Otsuka had reduced confidence in, and brought discredit upon the pharmaceutical industry and **a breach of Clause 2** was ruled.

Complaint received **13 March 2023**

Case completed **20 June 2024**