CASE AUTH/2209/2/09

PFIZER v LEO PHARMA

Promotion of Innohep

Pfizer complained about Leo Pharma's promotion of Innohep (tinzaparin sodium, a low molecular weight heparin) for extended use in the treatment of venous thromboembolism in patients with cancer. The claims at issue were referenced to Hull *et al* (2006), a direct, three month clinical comparison of Innohep vs an oral anticoagulant in cancer patients with acute symptomatic proximal vein thrombosis. There were three items at issue: a leavepiece, a cancer guidelines review and a journal advertisement. Pfizer also marketed a low molecular weight heparin, Fragmin (dalteparin sodium).

Pfizer noted that in inter-company dialogue Leo had submitted that there was no upper limit placed on the duration of Innohep therapy. However, Section 4.2 of the summary of product characteristics (SPC) stated that, for the treatment of deep vein thrombosis and pulmonary embolus Innohep should be given 'for at least 6 days and until adequate oral anticoagulation is established'. In line with clinical practice this clearly indicated that patients started on Innohep and gradually switched to oral anticoagulation over a few days (ie they did not remain on Innohep). However, if there was no transition to an oral anticoagulant then Pfizer did not consider the wording of the SPC allowed extended use of Innohep for venous thromboembolism in cancer, and as such extended treatment would be outside the current marketing authorization. Similarly the Innohep patient information leaflet (PIL) did not include guidance for cancer patients on extended use in the treatment of venous thromboembolism.

Pfizer alleged that Innohep did not have a marketing authorization for extended use and thus any promotion of the product for extended use in cancer associated venous thromoboembolism was in breach of the Code. Additionally, Pfizer considered that such activity might have significant safety implications for patients by encouraging unlicensed use of Innohep, particularly as there was no guidance for either health professionals or patients on the extended use of Innohep in patients with cancer associated venous thromboembolism in either the SPC or the PIL.

The Panel noted that the journal advertisement was headed 'Innohep – long term efficacy in treatment of [pulmonary embolism] and [deep vein thrombosis] in cancer patients' and that one page of the leavepiece, headed 'Thrombosis and Cancer', referred to 'Long-term Innohep'. The leavepiece featured a graph adapted from Hull *et al* which showed the cumulative incidence of recurrent venous thromboembolism over 300 days in cancer patients treated either with low molecular weight heparin or iv heparin/warfarin. The document reviewing the evidence and guidelines in cancer patients detailed the results from Hull *et al* and referred to the three month treatment period. It was stated that long-term Innohep was more effective than warfarin for preventing recurrent venous thromoboembolism in patients with cancer in proximal venous thrombosis. The document also gave brief details of UK guidelines on oral anticoagulation and two US guidelines on the treatment of venous thromboembolic disease. In a summary of the recommendations it was stated that the minimum duration of treatment with low molecular weight heparin was 6 months in the UK for the treatment of deep vein thrombosis and pulmonary embolism in patients with cancer. The US guidelines suggested 3-6 months' therapy for the treatment of deep vein thrombosis. For the treatment of pulmonary embolism one US guideline suggested 6-12 months' therapy and the other stated 3-6 months' therapy.

The Innohep SPC stated that therapy should be given 'for at least 6 days and until adequate oral anticoagulation is established'. There was no minimum duration of therapy stated in the Fragmin SPC. Sections 4.4 of both SPCs referred to the increased risk of hyperkalaemia with duration of therapy and the need to monitor plasma potassium particularly if therapy was prolonged beyond about 7 days. Pfizer had stated that the Medicines and Healthcare products Regulatory Agency (MHRA) required a specific licence for the extended use of Fragmin, in cancer patients with venous thromboembolism. No details were provided.

The Panel noted that although the Innohep SPC referred to therapy continuing 'for at least 6 days' there was no upper time duration given. There was an acknowledgement that therapy might be 'prolonged beyond about 7 days'. The Panel considered that although long-term therapy was not specifically referred to in the Innohep SPC there was nothing to suggest that it should not be administered for periods of longer than 6 days when there was a failure to establish adequate oral anticoagulation. The Panel considered that the claims relating to extended use were not inconsistent with the particulars listed in the SPC as alleged and ruled no breach of the Code.

Upon appeal by Pfizer, the Appeal Board noted that the Innohep SPC stated that therapy should be given 'for a least six days and until adequate oral anticoagulation is established'. There was no

upper time limit for the duration of therapy stated. Innohep had been granted a licence before long-term therapy had been contemplated. In that regard the Appeal Board considered that the data relating to side-effects and safety in the SPC was limited to that obtained only from the envisaged short-term (five to seven days) use in patients after surgery or during haemodialysis – not from long-term use in cancer patients. The Appeal Board noted Pfizer's submission that its product was indicated for extended use in a number of markets including the US. The Appeal Board noted that although clinical practice and published guidelines might support the long-term use of low molecular weight heparins in cancer patients it considered that, given the basis upon which the licence for Innohep was granted, promotion of the product for long-tern use was not in accordance with the terms of its marketing authorization and thus inconsistent with the particulars listed in the Innohep SPC. A breach of the Code was ruled.

Pfizer Limited complained about the promotion of Innohep (tinzaparin sodium) by Leo Pharma. Innohep was a low molecular weight heparin for the treatment of deep vein thrombosis and pulmonary embolus. There were three items at issue: a leavepiece (ref 1030/10191), a cancer guidelines review (ref 1030/10186) and a journal advertisement (ref 1030/10216) which had appeared in a number of oncology/cancer journals and the hospital edition of the BMJ.

Pfizer marketed Fragmin (dalteparin sodium), a low molecular weight heparin for the treatment of venous thromboembolism presenting clinically as deep vein thrombosis, pulmonary embolus or both.

COMPLAINT

Pfizer complained about claims relating to the extended use of Innohep for the treatment of venous thromboembolism in patients with cancer. The claims were referenced to Hull *et al* (2006), a clinical comparison of the extended use of Innohep vs a vitamin-K antagonist (oral anticoagulant) in cancer patients with acute symptomatic proximal vein thrombosis. Patients were randomized to receive 3 months of either treatment option. The study was not designed nor had tested a transition between low molecular weight heparin followed by a vitamin-K antagonist, but it had tested the direct head-to-head efficacy of Innohep and vitamin-K antagonist.

In inter-company dialogue Leo had stated that Innohep was licensed for the 'Treatment of deep vein thrombosis and of pulmonary embolus', with posology stating that treatment could be given for at least 6 days [following diagnosis] and until adequate oral anticoagulation was established. Leo submitted that there was no upper limit placed on the duration of Innohep therapy.

Section 4.2 of the Innohep summary of product characteristics (SPC) stated that, for the treatment of deep vein thrombosis and pulmonary embolus Innohep should be administered '…for at least 6 days and until adequate oral anticoagulation is established'. In line with clinical practice this wording clearly indicated that patients started on Innohep and gradually switched to oral anticoagulation over a few days (ie they did not remain on Innohep). However, if there was no transition to oral anticoagulation treatment then Pfizer did not consider the wording of the Innohep SCP allowed extended use of the product for venous thromboembolism in cancer, and as such extended treatment would be outside the current marketing authorization. Similarly the Innohep patient information leaflet (PIL) did not include guidance for cancer patients on extended use in the treatment of venous thromboembolism.

In inter-company dialogue Pfizer had referred to its status with the Medicines and Healthcare products Regulatory Agency (MHRA) regarding a licence application for the extended use of Fragmin, based on the CLOT study (Lee *et al* 2003), in patients with cancer associated venous thromboembolism. Pfizer was in ongoing dialogue with the MHRA regarding its licence application.

Pfizer submitted that as the MHRA required a specific licence for the extended use of Fragmin in this patient group, then by the same analogy Innohep did not have a marketing authorization to allow promotion of extended use in this patient population. Pfizer thus alleged that any materials or activities that promoted the use of Innohep for extended use in cancer associated venous thromoboembolism were in breach of Clause 3.2 of the Code.

Additionally, Pfizer considered that this promotional activity might have significant safety implications for patients by encouraging unlicensed use of Innohep, particularly as there was no guidance for either health professionals or patients on the extended use of Innohep in patients with cancer associated venous thromboembolism in either the SPC or the PIL.

RESPONSE

Leo explained that cancer patients presented a number of unique challenges in the treatment of thromboembolism. Conventional treatment with warfarin was difficult in these patients because of the need to regularly monitor the anticoagulant effect, drug interactions, recurrent thrombosis, longer admission times and disruption of invasive interventions due to normalisation of the International Normalised Ratio (INR).

A retrospective review of the practical problems and resource implications of the use of warfarin in cancer patients with venous thromboembolism (n=55), reported that 24% (n=13) of patients with metastatic disease were changed from warfarin to

low molecular weight heparin (Morris *et al* 2007). Patients were switched due to: pulmonary embolism (n=2); propagation of deep vein thrombosis (n=2) and improved patient care by facilitating home based care thus minimising hospital visits and invasive blood tests (n=9). This study also reported that there were 382 days' ward visits attributable to warfarin monitoring, with 1,379 coagulation tests performed and 21 invasive interventions required disruption of anticoagulation, with potentially longer admissions and delays in procedure due to normalisation of the INR.

Hull *et al* was a multi-centre, randomized, open-label clinical trial of acute deep vein thrombosis therapy in cancer patients to compare once daily subcutaneous Innohep with usual care warfarin therapy for 3 months. There were statistically significantly more cases of recurrent venous thromboembolism in the warfarin group compared with the Innohep group.

The 3 month duration of therapy used by Hull *et al* was in line with the three major published guidelines for the treatment of acute deep vein thrombosis in cancer patients which stated that it should be given for either up to 6 months (British Committee for Standards in Haematology (BCSH) Guidelines 2005) or for 3-6 months (US National Comprehensive Cancer Network (NCCN) 2006 and American College of Chest Physicians (ACCP) Guidelines 2008).

In the UK BCSH Guidelines 2005, the recommendation for cancer was 'Warfarin is generally inferior to therapeutic low molecular weight heparin (LMWH) for treatment of [venous thromboembolism] in patients with cancer'.

Leo submitted that Innohep was licensed for the 'Treatment of deep vein thrombosis and of pulmonary embolus', with posology stating that treatment should be given for at least 6 days [following diagnosis] and until adequate oral anticoagulation was established. There was no upper limit on the duration of Innohep therapy. Therapy should be maintained for at least 6 days and until oral anticoagulation was established. However, if progression to oral anticoagulation was not the longer term therapy of choice then the duration of therapy should be supported by clinical evidence and further endorsed by clinical guidelines. In relation to the PIL wording on duration of use, the 'How to use' section stated 'You will have one dose of Innohep each day for at least 6 days'. This was fully aligned with the duration of therapy in question and with the product SPC.

With regard to Pfizer's submission that the MHRA required a specific licence for the use of Fragmin in this group, Leo understood that Pfizer's application was initiated and submitted proactively rather than in response to a specific request or requirement from MHRA.

In conclusion Leo submitted that clinical evidence and clinical guidelines suggested that in this treatment group, low molecular weight heparins (such as Innohep) should be continued for at least 3 months, in preference to oral anticoagulation, to optimise the efficacy and safety outcomes for cancer patients. No significant safety implications had been identified for Innohep used in this way. The Innohep SPC did not preclude use in this way as it allowed for continuation of therapy until oral anticoagulation was established. Leo therefore strongly asserted that its current promotion of Innohep in cancer patients with venous thromboembolism was within the terms of the Innohep marketing authorization and consequently that it was not in breach of Clause 3.2.

PANEL RULING

The Panel noted that the journal advertisement headline claim 'Innohep – long term efficacy in treatment of [pulmonary embolism] and [deep vein thrombosis] in cancer patients' was referenced to Hull *et al*. Page 8 of the leavepiece was headed 'Thrombosis and Cancer' and referred to 'Long-term Innohep'. The page featured a graph adapted from Hull *et al* which showed the cumulative incidence of recurrent venous thromboembolism over 300 days in cancer patients treated either with low molecular weight heparin or iv heparin/warfarin. The document reviewing the evidence and guidelines in cancer patients detailed the results from Hull *et al* and referred to the three month treatment period. It was stated that long-term Innohep was more effective than warfarin for preventing recurrent venous thromoboembolism in patients with cancer in proximal venous thrombosis. The document also gave brief details of the UK BCSH guidelines on oral anticoagulation and the US NCCN and ACCP guidelines on the treatment of venous thromboembolic disease. In a summary of the recommendations it was stated that the minimum duration of treatment with low molecular weight heparin was 6 months in the UK for the treatment of deep vein thrombosis and pulmonary embolism in patients with cancer. The US guidelines suggested 3-6 months' therapy for the treatment of deep vein thrombosis. For the treatment of pulmonary embolism the NCCH guidelines suggested 6-12 months' therapy and the ACCP guideline stated 3-6 months' therapy.

The Panel noted that Section 4.2 of the Innohep SPC, Posology and Method of Administration, stated that therapy should be given 'for at least 6 days and until adequate oral anticoagulation is established'. There was no minimum duration of therapy stated in the Fragmin SPC. Sections 4.4 of both SPCs referred to the increased risk of hyperkalaemia with duration of therapy and the need to monitor plasma potassium particularly if therapy was prolonged beyond about 7 days. Pfizer had stated that the MHRA required a specific licence for the extended use of its product,

Fragmin, in cancer patients with venous thromboembolism. No details were provided.

The Panel noted that although the Innohep SPC referred to therapy continuing 'for at least 6 days' there was no upper time duration given. There was an acknowledgement in Section 4.4 that therapy might be 'prolonged beyond about 7 days'. The Panel considered that although long-term therapy was not specifically referred to in the Innohep SPC there was nothing to suggest that it should not be administered for periods of longer than 6 days when there was a failure to establish adequate oral anticoagulation. The Panel considered that the claims relating to extended use were not inconsistent with the particulars listed in the SPC as alleged and ruled no breach of Clause 3.2.

APPEAL BY PFIZER

Pfizer noted that the Innohep SPC for the treatment of deep vein thrombosis and pulmonary embolus stated that treatment should be given for at least 6 days **and** until adequate oral anticoagulation was established. It did not state **or** until adequate oral anticoagulation was established.

Standard practice for treatment of deep vein thrombosis was to commence low molecular weight heparin and oral anticoagulation (most commonly warfarin) simultaneously because warfarin usually took 5-7 days to become therapeutic. Once warfarin became therapeutic the low molecular weight heparin was stopped.

Pfizer noted warfarin was a difficult medicine to use, particularly in cancer patients for all the reasons outlined above. This was the rationale for designing the 3 month Hull *et al* study (using Innohep as the heparin) and the 6 month CLOT study (Lee *et al*) (using Fragmin as the heparin). In both studies the comparator arm (or usual care) was short-term heparin which was stopped as soon as the oral anticoagulation became therapeutic. Both studies demonstrated a reduction in recurrence of thrombosis in the active arm and these data had been reflected in several haematology and oncology guidelines specifically for treatment in patients with cancer.

Nevertheless, Pfizer alleged that medicines could not be promoted simply because clinical data and guidelines supported an indication. The SPC must be updated with the new information to gain this indication. The Innohep SPC only allowed for treatment for at least 6 days and until adequate oral anticoagulation was established; a licence variation would be required in order to promote extended treatment with Innohep instead of using oral anticoagulation as per Hull *et al*.

Pfizer had proactively approached the MHRA to apply for a licence variation for Fragmin based on the 6 month data from the CLOT study. The application was in its final stages but throughout the process over many months the MHRA had indicated repeatedly that granting an extended use licence was not straightforward and was a significant departure from the standard practice of short-term use until effective oral anticoagulation was achieved. The application had required detailed risk benefit analysis of extended use and particular thinking had been required around risk minimisation for patients who were likely to self-inject over an extended period.

In summary, whilst Pfizer accepted there were robust data and clinical guidelines supporting the extended use of low molecular weight heparin in cancer associated deep vein thrombosis, it did not agree that Leo could promote this use based on its current SPC without applying for a licence variation. The key wording was the fact that the Innohep SPC stated that treatment should be given for at least 6 days **and** until adequate oral anticoagulation was established. It did not state **or** until adequate oral anticoagulation was established. The SPC wording clearly indicated the intention to transition to oral therapy. Where no such intention existed, as in Leo's promotional material, then this was outside the Innohep licence. For these reasons Pfizer repeated its allegation of a breach of Clause 3.2.

COMMENTS FROM LEO

Leo was pleased that Pfizer had accepted that there were robust data and clinical guidelines to support the continued use of low molecular weight heparins in preference to switching to treatment with warfarin in patients with cancer associated deep vein thrombosis.

Leo understood the difficulty that Pfizer had with the CLOT study (Lee *et al*). Although this study initiated treatment with the licensed dose of 200 IU/kg of Fragmin (dalteparin sodium), the dose was reduced to approximately 150 IU/kg after the first month. Such a step type treatment regimen was not within the SPC for Fragmin and thus the requirement for a licence variation would apply.

Leo submitted that it had only promoted Innohep for the treatment of venous thromboembolism using the approved treatment dose of 175 IU/kg which was the dose used in Hull *et al*. As the Panel noted, the Innohep SPC did not give an upper time limit for the duration of treatment if it was not followed by oral anticoagulation, thus treatment with a low molecular weight heparin for 3-6 months, as supported by the robust data and clinical guidelines agreed by Pfizer, was not inconsistent with the Innohep SPC. As the Panel also noted within Section 4.4 of the Innohep SPC, advice was given on management if treatment was extended beyond seven days.

Leo therefore submitted that its current promotion of Innohep in patients with cancer associated venous thromboembolism was within the terms of

the marketing authorization for Innohep and, consequently, it was not in breach of Clause 3.2.

FINAL COMMENTS FROM PFIZER

Pfizer alleged that the use of low molecular weight heparins for extended duration in oncology patients with venous thromboembolism was a completely new regimen for these medicines. Any variation in the recommended dosage of the medicine was only one aspect of the overall new regimen, and other important aspects which also needed to be considered included the duration of treatment and the types of patients receiving the medicines. The MHRA had clearly indicated to Pfizer that the duration of therapy and the patient population were crucial determinants of the risk benefit profile.

The Fragmin (Lee *et al*) and Innohep (Hull *et al*) clinical trials that evaluated the effectiveness of these medicines in an oncology population were designed as head-to-head trials comparing short-term low molecular weight heparins transitioning onto warfarin (usual care) vs extended use of low molecular weight heparins throughout the 3-6 month study duration. The latter was the alternative and a new regimen to the current product SPC, and therefore Pfizer proactively approached the MHRA to apply for a licence variation for Fragmin.

For the reasons mentioned above Pfizer alleged a breach of Clause 3.2.

APPEAL BOARD RULING

The Appeal Board noted that Section 4.2 of the Innohep SPC, Posology and Method of Administration, stated that therapy should be given 'for a least six days and until adequate oral anticoagulation is established'. There was no upper time limit for the duration of therapy stated. Leo's representatives at the appeal confirmed that Innohep had been granted a licence before long-term therapy in any patient group had been contemplated. In that regard the Appeal Board considered that the data relating to side-effects and safety in the SPC was limited to that obtained only from the envisaged short-term (five to seven days) use in patients after surgery or during haemodialysis – not from long-term use in cancer patients. The Appeal Board noted Pfizer's submission that its product was indicated for extended use in a number of markets including the US. The Appeal Board noted that although clinical practice and published guidelines might support the long-term use of low molecular weight heparins in cancer patients it considered that, given the basis upon which the licence for Innohep was granted, the promotion of Innohep for long-tern use was not in accordance with the terms of its marketing authorization and thus inconsistent with the particulars listed in the Innohep SPC. A breach of Clause 3.2 was ruled. The appeal was successful.

During its consideration of this case the Appeal Board noted that, regardless of the Innohep marketing authorization, the three month data (the primary outcome data from Hull *et al*) relied upon by Leo to substantiate its claims showed no statistically significant difference between Innohep and usual care (short-term low molecular weight heparin with a transition to warfarin therapy) with regard to bleeding complications during the three month treatment interval. Study medicines were discontinued at 12 weeks unless oral anticoagulation was indicated. At 12 month follow-up there was a statistically significant difference in recurrent venous thromboembolism between the two treatment groups in favour of Innohep (p=0.044). The Appeal Board requested that Leo be advised of its concerns.

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