NOVARTIS' PATENT ON A TRANSDERMAL THERAPEUTIC SYSTEM FOR THE ADMINISTRATION OF RIVASTIGMINE FOUND INVALID, CLEARING THE WAY TO 'GENERICS' TO THE EXELON PATCH

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The High Court of England and Wales (Patents Court) has ruled that Novartis' patent to the transdermal therapeutic system ('TTS') of its Exelon Patch is invalid, for obviousness and added matter. The decision clears the way for the launch of 'generic' rivastigmine patches. Had the patent been valid, the defendants' (Focus, Actavis and Teva) patches would have infringed.

Novartis' Patent

Novartis' European patent number EP (UK) 2 292 219, entitled 'Transdermal therapeutic system for the administration of rivastigmine' ('the patent'), claimed a TTS. Broken into integers, claim 1 was to the following:

> *[1] Rivastigmine for use in a method of preventing, treating or delaying progression of dementia or Alzheimer's disease,*
>
> *[2] wherein the rivastigmine is administered in a TTS and*
>
> *[3] the starting dose is that of a bilayer TTS of 5cm² with a loaded dose of 9mg rivastigmine,*
>
> *[4] wherein one layer: has a weight per unit area of 60g/m² and the following composition: …*
>
> *[5] and wherein said layer is provided with a silicone adhesive layer having a weight per unit area of 30g/m² according to the following composition …*

Technical Background

In the Patents Court, Arnold J considered the identity and knowledge of the 'person skilled in the art'. The relevant date was 1 December 2005 (the claimed priority date).

It was technical background and 'common general knowledge' ('CGK') that four drugs ('active pharmaceutical ingredients' ('APIs')) were being used to treat mild to moderate Alzheimer's disease ('AD'), three of which were AChE inhibitors. One of these was rivastigmine (brand name Exelon, developed by Sandoz/Novartis). Another was donepezil.

Rivastigmine was administered orally twice daily, at 1.5mg to 6mg per dose. The minimum therapeutically effective dose was 3mg twice daily. Patients were 'titrated' up gradually from lower doses to enable them to acquire tolerance to side effects.

Donepezil only required a single daily dose.

All three AChE inhibitors were associated with cholinergic effects such as nausea, vomiting and diarrhoea. Tolerance to the drugs tended to reduce with even a short break in treatment.

The 'Skilled Team'

The patent, explained Arnold J, was addressed to a skilled team which was interested in developing a new formulation for rivastigmine. This included a formulator skilled in the

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transdermal administration of drugs and a clinician working in the field of dementia, who would call upon a pharmacologist where necessary.

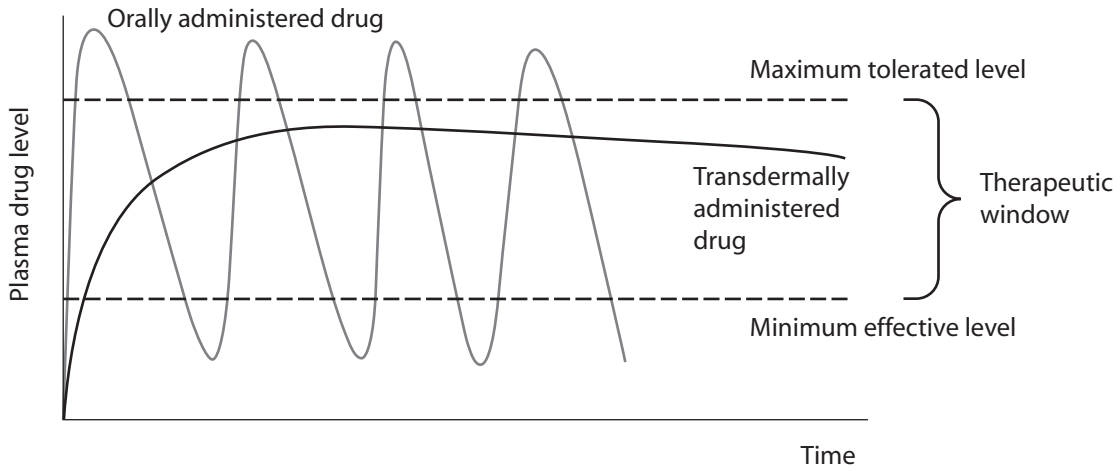
Common General Knowledge

The CGK also included the following:

- Oral administration should be with morning and evening meals.
- Administration with food:
  - increased by approximately 30 per cent the area under the concentration-time curve (AUC) – the AUC reflects the actual body exposure to a drug after administration – and this was considered 'puzzling',
  - lowered C_{max} (a measure of the peak plasma concentration of the drug), and
  - delayed absorption (t) (the time at which C_{max} was reached) by 90 minutes.
- Administration by transdermal patch had a number of advantages over oral formulations, including: bypassing the gastrointestinal (GI) tract (avoiding locally mediated side effects in the GI tract); once daily dosing; and a smoother delivery curve (see below). Of 28 approved transdermal patches none was for the treatment of AD.
- Transdermal administration also had some disadvantages, including: only a limited number of APIs being suitable for such administration; it being more expensive and time-consuming to develop; the onset of treatment being slower than with oral formulations; and potential for local skin irritation.
- A transdermal patch included an outer backing layer, typically impermeable to water, a preparation containing the API along with excipients, and a release liner which was removed before the patch was applied to the skin.
- Once an API was identified as being suitable for patch delivery, a target dose would be given to the formulator, generally quantified in terms of a target AUC, typically the AUC in 24 hours (AUC_{24h}). Usually, the target AUC_{24h} would correspond to the AUC_{24h} for the oral form. Prototypes would be developed and tested, *in vitro* and *in vivo*, and assessed upon the amount of API released from the patch.

Arnold J agreed with the defendants that it was CGK that (i) the side effects of rivastigmine were caused by sharp peaks in drug levels, indicated by short t_{max} and high C_{max}, and (ii) the recommendation to administer with food was given in order to improve tolerability. The defendants had cited 11 publications in support of these points being CGK. The skilled person would have been aware that these were a 'reasonable hypothesis' even though there was 'no firm evidence to support the hypothesis'.

Further, even if not CGK, at the outset of a project to develop a new formulation for rivastigmine, it would have been an obvious step for the skilled team to perform a short and focused literature search. This would have thrown up some or all of the papers relied upon by the defendants, from which the same conclusions would have been drawn.



Construction

The defendants argued that the claim should be construed as restricted to the administration of rivastigmine via a TTS having the structure and composition specified in integers [3], [4] and [5] of the claim.

Arnold J disagreed. In his view, the defendants' construction did not engage with the language of the claim, and in particular the language 'the starting dose is that of' in [3]. The natural meaning of those words was that the method of administration involved a starting dose which was the same as that of a TTS having the specified characteristics. If the patentee had intended to claim the administration of rivastigmine via a TTS having the structure of example #2 (TTS #2), then those words would be redundant.

Instead, Arnold J accepted Novartis' construction, which was that the claim had three components:

(1) to rivastigmine for use in treating dementia or AD;

(2) the rivastigmine being administered via a TTS; and

(3) the 'starting dose' of rivastigmine administered by TTS being the dose released by a reference TTS which was specified in integers [3], [4] and [5] (that is, a reference patch described in example #2).

The judge said that although the benefits of the invention were obtained by using the structure of TTS #2, the claim was not limited to use of a TTS having such a structure.

As regards the meaning of 'starting dose', this referred (as Novartis contended) to the dose of rivastigmine with which treatment of a patient was started. This was quantified in terms of the mass of the drug released over the period of application of the TTS, typically 24 hours (for example, 4.6mg/24 hrs). The defendants' contention that 'starting dose' meant AUC_{24h} was rejected, AUC being a measure of bioavailability, not dose.

The parties agreed that the claim was not limited by any particular number of titration steps, any particular level of efficacy or any particular level of side effects.

Added Matter

Arnold J described the invention disclosed in Novartis' application as having two main aspects:

> *The first concerns a three-layer TTS. The second aspect concerns a TTS providing C_{max} and AUC_{24h} values of rivastigmine within the broad ranges disclosed in the claimed application.*

The description of the patent (a divisional) was broadly similar, but with a number of differences:

> *… First, whereas the Application said that '[t]he present invention provides' a TTS comprising a backing layer, a reservoir layer and an adhesive layer, and so on, the Patent instead refers to 'one embodiment [of] the present disclosure' of the Patent doing so, to 'a TTS according to the disclosure' or to 'a TTS as used in the invention'… Similarly, whereas in the Application there was reference to preferred embodiments having particular characteristics in relation to e.g. the reservoir or silicone adhesive layer, in the Patent the corresponding passages now refer to preferred embodiments in which the TTS comprises such a reservoir or silicone adhesive layer …*
>
> *Secondly, the extensive definition of 'active ingredient' contained in the Application has been deleted from the Patent.*
>
> *Thirdly, the passage concerning better tolerability … is no longer followed by the consistory clauses concerning the specified pharmacokinetic profiles.*
>
> *Fourthly, the passage referring to the starting dose … now refers to the TTS 'used in', rather than 'of', the invention.*

The effect of this, Arnold J concluded, was that the patent informed the skilled reader for the first time that:

(1) the invention lay in the selection of a particular starting dose for rivastigmine administered via a TTS for the treatment of AD;

(2) the dose delivered by the 5cm² TTS of example #2 should be used as the starting dose; and

(3) this starting dose may be obtained using a TTS which does not have the structural and compositional features disclosed in the application.

The judge said that Novartis really had no answer to the first of these points.

Regarding the second point, all that the reader of the application was explicitly told about the starting dose was that the TTS of the invention may allow a higher starting dose. The skilled clinician would appreciate that whether this could be achieved would depend on whether the higher starting dose was tolerated by patients, but there was no information in the application about the level of side effects experienced by patients.

This meant that the claim in the patent was an intermediate generalisation, because it took the feature of the starting dose delivered by the 5cm² TTS #2 stripped of its context in the example, when it would not be clear to the skilled team that that feature was generally applicable or that the other features of the example were inessential to the invention.

Regarding the third point, Arnold J noted that previously, the structure and composition of the TTS were presented as the core of the invention. It was irrelevant that although the claim covered a starting dose obtained by TTSs having different structural and compositional features, it did not disclose it as such. (That was not the test for added matter.)

Consequently the patent was invalid for added matter.

Obviousness

At the trial, the defendants relied on a single piece of prior art, a US patent (Novartis owned), which disclosed in example 4 a TTS having the same structure and composition as that of the TTS #2, but with double the loaded dose per cm².

It was not disputed that it would be straightforward for the skilled formulator to make various patches of differing size having the disclosed structure and composition, including a 5cm² patch with the loaded dose of TTS #2. Nor was there much dispute about motivation, namely to get once daily administration using a patch, or that the starting point for the skilled team would be to develop a patch which matched the AUC_{24h} of the existing oral formulation of Exelon capsules.

Novartis contended that the skilled team would administer a starting dose using a patch which matched that of the starting dose in the oral regimen (that is, less than half that released by the 5cm² TTS #2), and then titrate it up in a similar way to the oral regimen.

On the other hand, the defendants' position was that it would be obvious to try the dose released by the 5cm² TTS #2 as the starting dose in a small scale clinical trial, because:

(1) The US patent taught that the size of the patch could be determined using routine bioavailability tests; these would reveal that the dose released by the 5cm² TTS #2 patch delivered an AUC_{24h} approximately equal to that of the 6mg daily oral dose (that is, the minimum therapeutically effective dose). They would then find that it was well tolerated.

(On this approach, Arnold J noted that while the US patent did not in terms instruct the skilled team to omit the sub-therapeutic dose, 'it cannot be inventive to do exactly what it does say'.)

(2) If the skilled team were concerned about tolerability, they would appreciate that delivery by a patch would smooth the plasma profile and hence provide a longer t_{max} and lower C_{max} than the oral formulation. Based on CGK about the food effect, the skilled team would think it reasonably likely that the dose released by the 5cm² TTS #2 would be sufficiently well tolerated to be administered as the starting dose.

(On this approach, Arnold J commented that '[i]ndeed, the data in the Patent show that the C_{max} of a patch matched to the AUC_{24h} of a 3mg bid dose would be lower than the C_{max} of the 1.5mg bid dose'. He also noted that while the side effects of rivastigmnine could be unpleasant, they were generally not severe and the inventors were not put off trying the claimed dose as the starting dose by the potential side effects. Nor was there anything to suggest that they were a risk which the skilled team would not be prepared to countenance.)

Arnold J concluded that for both of the reasons advanced by the defendants, it would have been obvious to try the dose released by the 5cm² TTS #2 in a small-scale clinical trial. The skilled team would have had a sufficient expectation of success to warrant doing so. Consequently the patent was invalid for lack of inventive step.

Insufficiency

Having succeeded in showing the patent was obvious, the defendants' obviousness/insufficiency squeeze fell away.

The defendants also argued that if the claim extended to any TTS that delivered a starting dose which was that of the 5cm² TTS #2, then it was insufficient. This was because (1) it would cover 'burst release' formulations which would not have the required tolerability, and (2) the patent did not enable the skilled team to determine whether any other TTS delivered the same starting dose or not.

These challenges failed too. On the first point, Arnold J said: 'A patent is not insufficient merely because it is possible to imagine a way of implementing the claim badly if in practice that is not something that the skilled person would do.'

On the second point, Arnold J held that on the expert witnesses' evidence, the skilled team would be able to select an appropriate statistical test to determine whether the same TTS was delivered.

Infringement

Infringement was dealt with briefly, each of the alleged infringing patches being bioequivalent to Novartis' Exelon patch. Arnold J concluded that if the patent had been valid, the defendants would have infringed it.

Comment

This decision underlines the risks of 'adding matter' in the course of the conceptual development of an invention, after the filing of the application for the patent. The risk would tend naturally to be greater for divisional applications, such as the patent in this case, where there can be a relatively long interval in time between the filing of the application and the grant of the patent.

Interestingly, both Novartis and the defendants seem to have presented their cases on obviousness on the basis of the test being whether the skilled person 'would' have made the invention. The finding that there was no inventive step perhaps reflects in part the level of expertise of the pharmaceutical 'skilled team' in this case. It perhaps also reflects the difficulty of demonstrating inventiveness for more incremental stages in research and development. Before the Exelon Patch, there had never been an AD therapy delivered by a TTS, but this did not make the development of the first patch inventive over matter which had already been made available to the public.