Neutral Citation Number: [2008] EWHC 1422 (Pat)

Case No: HC0700 572

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 30/06/2008

Before :

THE HON MR JUSTICE FLOYD

- -

Between :

ACTAVIS UK LIMITED	**Claimant**
- and -	
JANSSEN PHARMACEUTICA N.V.	**Defendant**

- -
- -

Roger Wyand QC and Piers Acland (instructed by **Bird & Bird**) for the **Claimant**
Daniel Alexander QC and James Whyte (instructed by **Linklaters LLP**) for the **Defendant**

Hearing dates: 14th -15th May, 19th May

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Judgment

Mr Justice Floyd :

1. Actavis UK Limited seeks revocation of European Patent No 0 334 429 ("the Patent") which is in the name of Janssen Pharmaceutica N.V. ("Janssen"). The Patent concerns the stereochemistry of an important blood pressure drug, nebivolol. Janssen has applied to amend certain claims of the Patent. Actavis maintains that the Patent, even if so amended would remain invalid for lack of novelty and lack of inventive step.

The background and the common general knowledge

2. There is very little dispute about the relevant technical background. I set out below the matters which formed part of the relevant common general knowledge.

Hypertension and anti-hypertensive agents

3. Hypertension is the technical name for high blood pressure. Three main classes of agent were used to treat hypertension in 1988: β-blockers, diuretics and vasodilators.

4. **β-blockers** are so named because they block the action of endogenous compounds such as adrenaline on certain receptors in the body, the so-called β-adrenergic receptors. There are two sub types of β-receptor: β_1 and β_2. The former are to be

5. Early β-blockers were non-selective in that the drug would block both β_1 and β_2 receptors. This meant that if these early drugs were used to treat angina (in the heart muscle) in patients who also had asthma, there was the potential for serious side effects, as the receptors in the lung (undesired) would be blocked along with the receptors in the heart (desired). The second generation of β-blockers therefore focussed on drugs with β_1 selectivity. Drugs with a high ratio of β_1 to β_2 activity were therefore developed.

6. The precise mechanism of action of β-blockers in lowering blood pressure was not fully elucidated in 1988. It was, however, known that they reduced cardiac output (both heart rate and force of contraction) but were also associated, at least in the short term, with vasoconstriction, which acts as a drag on the blood pressure lowering effect of the β-blocker. So use of a β-blocker might not be associated with an immediate drop in blood pressure.

7. In 1988 the focus of drug development was a third generation of β-blockers, in which the compound has additional pharmacological properties.

8. Labetalol was one of the first of this third generation. It combined non-selective β-blockade with α-adrenergic receptor blockade (blocking the vasoconstrictor effects of noradrenaline). It was marketed as a racemate of four stereoisomers (see below). The α- and β-blockade reside principally in separate isomers. This aspect of the drug attracted particular interest at the time it was launched.

9. **Diuretics** increase the rate at which sodium is excreted from the body in urine. This has the effect of reducing the amount of water and sodium in the body, which reduces the pressure on the walls of the blood vessels.

10. **Vasodilators** dilate blood vessels. The result is that they reduce vascular resistance and hence blood pressure, because the diameter of the blood vessels increases.

Step care management

11. The treatment of hypertension with β-blockers together with a diuretic and/or vasodilator, known as "**step care**" management, was well known. The rationale of this approach is to alleviate the body's natural response to a fall in blood pressure when treated with β-blockers alone. A vasodilator will counter this effect.

Animal models

12. The standard animal models used for studying hypertension in 1988 included normotensive (normal blood pressure) and hypertensive (raised blood pressure) models. The blood pressure response in normotensive models would be smaller than the response seen in hypertensive models. There were various hypertensive models available. For rats, investigators would often clamp the renal arteries which had the effect of raising its blood pressure due to reducing blood supply to the kidney and increasing release of the hormone renin. Another model was a strain of rat from Japan known as the spontaneously hypertensive rat.

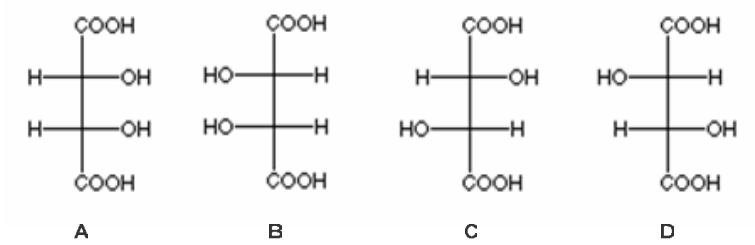
13. Tissue and organ preparations also existed and were used routinely for investigating β-blocker activity. The effect of the candidate drug would be assessed in its ability to counter the effects of a β-agonist on the tissue or organ in question.

Stereochemistry

14. The underlying concepts of stereochemistry have been described in a number of judgments: see e.g. the summary by Kitchin J in *Generics v Lundbeck* [2007] EWHC 1040 (Pat); [2007] RPC 32 at [12]-[17].

15. This case concerns the stereochemistry of compounds with more than one chiral centre. In theory a structure with a number of chiral centres, (say N), will exist as 2^N stereoisomers. So a structure such as that with which we are concerned in this case, with four chiral centres, could in theory have 16 stereoisomers. These stereoisomers consist of pairs of enantiomers, and there will be half of 2^N, or $2^{(N-1)}$ of these pairs. This is not always true, however, because in symmetrical molecules some of the stereoisomers will be the same.

16. A simple example is tartaric acid which has two chiral centres, and would therefore be expected to have four stereoisomers. In fact it has only three. In the diagram below enantiomers C and D are identical, because rotating one about the vertical axis makes it so:



17. Compunds which have chiral centres but which are in fact achiral are called meso compounds.

18. It is common ground that by the priority date there was pressure from the regulatory bodies including the FDA in the United States and the Japanese Ministry of Health to provide information about individual isomers.

The expert witnesses

19. Actavis called two expert witnesses, Professor John Reid and Professor Roger Newton as their expert pharmacologist and medicinal chemist respectively.

20. Professor Reid is Regius Professor of Medicine and Therapeutics and Head of the Division of Cardiovascular and Medical Sciences at the University of Glasgow. From 1987 to 1993 he was Editor in Chief of the Journal of Hypertension, a well known international publication in the field of high blood pressure research and its treatment. After qualifying in Medicine from Oxford University in the late 1960s he spent over 10 years at the Royal Postgraduate Medical School/Hammersmith Hospital in London training and conducting research in clinical pharmacology and new drug development. The principal interest of his group was blood pressure treatment and

the investigation and optimisation of β-blockers for the treatment of hypertension and other cardiovascular diseases. He was very well qualified to give evidence on the pharmacological aspects of the case.

21. Professor Newton was employed by Glaxo from 1971 to 1996 as a medicinal chemist in their chemistry division. Whilst at Glaxo, his areas of research included drugs for the treatment of cardiovascular, central nervous system and infectious diseases. For eight years he directed the company's global research into respiratory diseases. He joined Glaxo, as a senior research chemist and eventually became the director of the Chemical Research Division of Glaxo. He was also the Resident Medicinal Chemist in the Chemistry Department at the University of Cambridge from 1996 until 2005 and is Visiting Professor at the University of Sussex. His PhD was in the stereochemistry of compounds with bridgehead nitrogen atoms. Professor Newton has now given evidence in a large number of disputes concerning medicinal chemistry, a fact to which Mr Alexander QC (who appeared for Janssen with Mr James Whyte) drew attention in cross-examination. His evidence is not less useful as a result.

22. Janssen called only one expert, Professor Caldwell, who is the Dean of the Faculty of Medicine in the University of Liverpool. He played an important role in the re-emergence of stereochemistry as a factor in drug development. Since 1980 he has had an extensive consulting practice concerned with aspects of drug discovery and development including several programs related to hypertension and β-blockers.

23. Mr Wyand QC (who appeared for Actavis with Mr Piers Acland) said that there was a contrast between the oral evidence of Professor Caldwell and his expert report. There is some force in that, in that points taken firmly in his report seemed to dissolve under cross-examination. An example is his challenge in his second report to Professor Newton's assertion that the ratio of RSSS to SRRR isomers would be 1:1. Under cross-examination he said that if it were anything other than a racemate it would be surprising. Whilst I have not ignored his report, I have relied primarily on the oral evidence Professor Caldwell gave where there is a dispute between him and Professors Reid or Newton.

Witnesses of fact

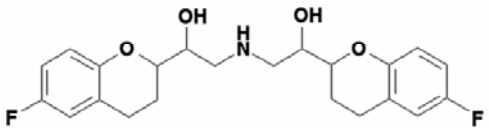
24. Actavis served fact witness statements from Professor Stephen Curry and Mr Martin Barkworth. Only the former was cross-examined (by video-link). He was a good witness.

25. Jannssen called Mr Woestenborghs to give evidence about a prior disclosure. He had no real recollection of the relevant events, and was understandably reluctant to accept that he had disclosed the invention, with the consequences that might entail. This led him, I thought, to cling on to somewhat unlikely explanations as to what might have happened.

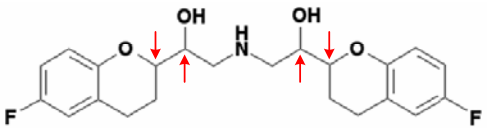
Nebivolol

26. Although not part of the relevant common general knowledge, it is worth noting what nebivolol is.

27. The general chemical structure of nebivolol is as follows:



28. This structure contains four chiral centres:



29. If all R and S combinations were distinct, the structure would embrace eight pairs of enantiomers. However, owing to the symmetry of the molecule around the central nitrogen atom, some of these configurations are duplicative. In summary, there are four pairs of enantiomers and two meso forms, a total of ten enantiomers.

30. Nebivolol comprises a 1:1 mixture of two isomers: the SRRR and the RSSS. The former is referred to as *d*-nebivolol and the latter as *l*-nebivolol.

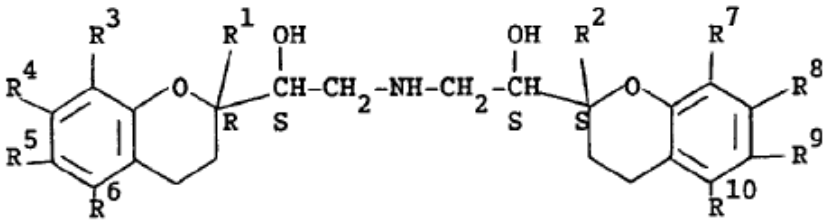
The Patent

31. The Patent has an unchallenged priority date of 23rd March 1988. It is entitled "Agents for lowering the blood pressure".

32. The Patent begins by saying that United States Patent No 4,654,362 (the "362 patent" cited as prior art in this case) describes a class of 2,2'-iminobisethanol derivatives having β-blocking activities. It identifies the discovery underlying the Patent in the following terms:

> It has now been found that a certain class of isomers of said bisethanol derivatives potentiate the activity of blood pressure reducing agents.

33. There follows a clause describing the invention in similar terms to the "use" claim of claim 1. The compounds for use in the invention are defined by a general formula (I) indicating the stereochemistry of the four chiral centres with the letters R and S:



(I),

34. The invention is said to be concerned with the use for the manufacture of a medicament for potentiating the effects of blood pressure reducing agents having

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