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Actavis v Eli Lilly

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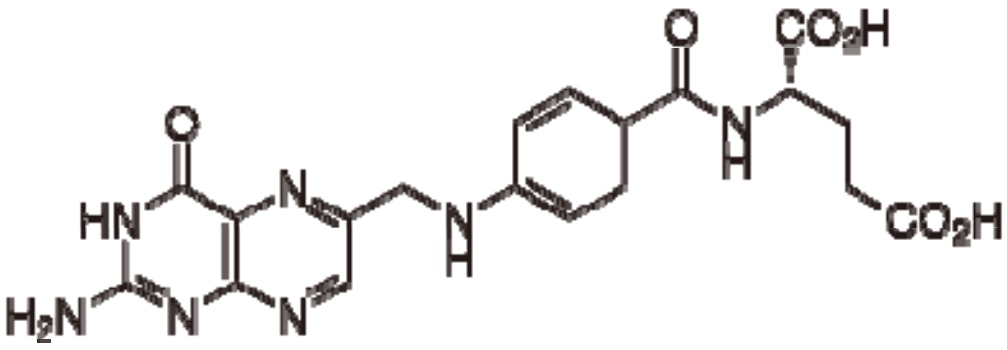
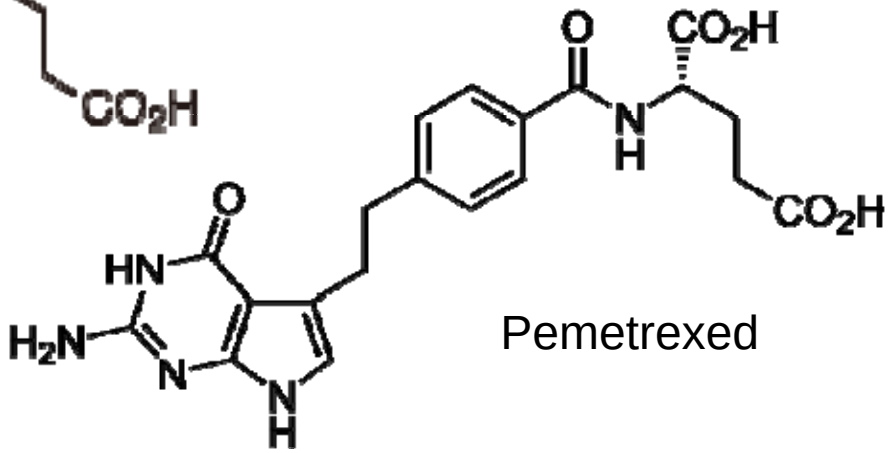
RSC Case Law Seminar

20 November 2014

Pemetrexed



Folic acid



Pemetrexed

Antifolate used in cancer treatment

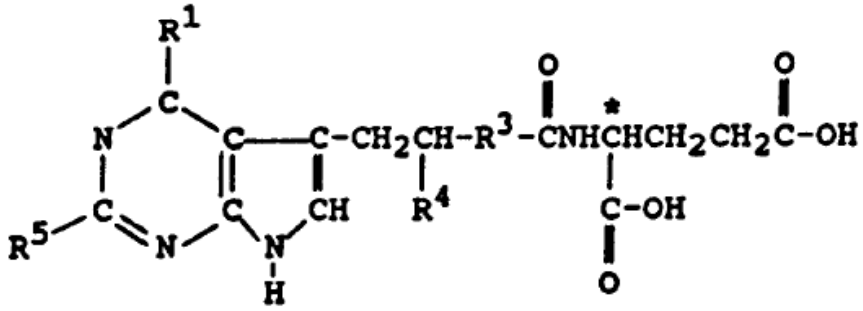
Alimta® - pemetrexed disodium

Global sales in 2013 = $2.7 billion

Pemetrexed – basic patent

Basic patent – EP 0 432 677

Claims relate to compounds of the following formula:



+ pharmaceutically acceptable salts.

Patent expired 10 December 2010

SPCs will expire 10 December 2015

Pemetrexed – follow-on patent

Follow-on patent EP 1 313 508

antifolate… ✗ Art 84

↓

Use of **pemetrexed…** ✗ Art 123(2)

↓

Use of **pemetrexed disodium…** → grant

Pemetrexed – follow-on patent

Claim 1 as granted:

> "*Use of **pemetrexed disodium** in the manufacture of a medicament for use in combination therapy for inhibiting tumor growth in mammals wherein said medicament is to be administered **in combination with vitamin B12** or [specific pharmaceutical derivatives of vitamin B12]*"

Claim 2 as granted:

> = claim 1 + specific **folic binding protein (FBP) binding agents** or physiologically available salt or ester thereof.

Claim 12 as granted = 2nd medical use version of cl. 2

Actavis v Eli Lilly [2014] EWHC 1511 (Pat)

Actavis v Eli Lilly

Actavis applied for DNI of EP ‘508 for:

- pemetrexed dipotassium
- pemetrexed diacid
- pemetrexed ditromethamine

DNI sought in respect of GB, FR, IT, and ES

Eli Lilly sued for threatened infringement in DE in 2013

Construction – skilled person

Who is skilled addressee for Swiss claim 1?

Eli Lilly:

- Swiss claim → method of treatment
- Skilled person = medical oncologist

Actavis:

- Skilled person = **team**, including
  - (i) A medical oncologist, and
  - (ii) Someone with experience in pre-formulation work, e.g. process chemist.

Arnold J agreed with Actavis = team

Construction – Improver Questions

(1) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no?

(2) Would this (i.e. that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art? If no, the variant is outside the claim. If yes?

(3) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim.

Construction – Question (1)

- "from the oncologist's perspective, source of the pemetrexed anion is immaterial, since it will not affect the efficacy or safety of pemetrexed…

- …from the chemist's perspective, it must be assumed… that pemetrexed diacid, dipotassium and ditromethamine are in fact all pharmaceutically acceptable and sufficiently soluble.

Answer = NO  Question (2)

Construction – Improver Questions

(1) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no?

(2) Would this (i.e. that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art? If no, the variant is outside the claim. If yes?

(3) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim.

Construction – Question (2)

Actavis – answer should be NO

- Oncologist would be uncertain of affect of substituting diacid for disodium salt on solubility or pharmaceutical acceptability, so would consult chemist.
- Chemist would be uncertain whether substitution would have material effect – most uncertain for diacid, less for ditromethamine, least for dipotassium.
- Irrelevant that the chemist would be reasonably confident that he could come up with an alternative counter-ion – that is not the question.

Construction – Question (2)

Eli Lilly – answer should be YES

- Skilled team knows variant has received regulatory approval
- Actavis mischaracterise the invention - invention concerns reducing toxic side effects of pemetrexed by co-administration of vitamin B12 and a folic protein binding agent.

Question (3)

Construction – Improver Questions

(1) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no?

(2) Would this (i.e. that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art? If no, the variant is outside the claim. If yes?

(3) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim.

Construction – Question (3)

Actavis – answer should be YES

- Pemetrexed disodium = specific, known compound
- Broad statements about “an antifolate”, narrow to “pemetrexed disodium”
- Claims refer to “pharmaceutical derivative” of vitamin B12, and contemplates use of “a physiological salt or ester” of selected FBP binding agent
- Reasonable for chemist to assume pemetrexed disodium because only compound made and tested

Construction – Question (3)

- Skilled team appreciate that there are a number of reasons for limiting to pemetrexed disodium: e.g.
  - cover commercial embodiment (Alimta)
  - ensure claims are supported
  - ensure fast grant
- **Prosecution history** – clear that Eli Lilly attempted to obtain broader claims, and simply narrowed to pemetrexed disodium to obtain rapid grant
- If claims construed as Lilly contend, invalid for added matter and/or insufficiency

Construction – Question (3)

Eli Lilly – answer should be NO

- Actavis engaging in “meticulous verbal analysis”
- Obvious to the skilled team that different suitable form of pemetrexed would work
- Prosecution history does not assist – application always included claims in which antifolate was pemetrexed disodium. Fact that broader claims were abandoned sheds no light on meaning of “pemetrexed disodium”
- Validity of the patent is not in question

Construction

Arnold J: answer is yes (i.e. variants do not fall within claims)

> *“[a]ny other conculsion would fail to give effect to the Protocol and would be tantamount to treating the claims as a mere guideline”*

Construction – prosecution history

Arnold J

"*In some cases, perhaps not very many, the prosecution history is short, simple and shows clearly why the claims are expressed in the manner in which they are to be found in the granted patent and not in some broader manner. In such a situation, there is no good reason why the court should shut its eyes to the story told by the prosecution file.*"

"*… I consider [the prosecution history] supplies a clear answer to the question why the claims are limited to pemetrexed disodium*"

German decision

Düsseldorf Regional Court reached different conclusion:

- pemetrexed dipotassium - no literal infringement, but infringement on basis of doctrine of equivalents.

Arnold J – "*I am unable to agree with its conclusion with regard to pemetrexed dipotassium*"

FR, IT, and ES designations

Expert evidence provided useful summaries of claim construciton in FR, IT and ES (specifically, doctrine of equivalents and use of prosecution history)

Arnold J concluded none of variants fell within claims

Conclusion

Direct infringement? ✗

Indirect infringement? ✗

- Alimta is reconstituted in 0.9% NaCl solution then diluted before injection
- Actavis admit their drug will be prepared in same way, with the same additional ingredients

Conclusions

- More use of prosecution history as an aid to construction?

- Improver questions back in fashion?

QUESTIONS?

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A BIG thank you to Paul Dunne
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