

**CLINICAL INNOVATION:** Fair & Effective Incentives for New Uses of Established Drugs

## Examples of Success: The Lyrica Story in Denmark

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**Presenter:** Sture Rygaard *Partner, Plesner*

**Panellists:**

- Dr Ute Kilger *Boehmert & Boehmert*
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- Dr Trey Powers *Sterne Kessler Goldstein Fox PLLC*

### Second Medical Use Patents in Denmark – the Lyrica® Story and SMUs in Tenders

- enforcement in harmony or conflict with the regulatory system?

Clinical Innovation and SMU Conference –  
Georgetown Law Center, Washington DC

Sture Rygaard, *Plesner Advokatpartnerselskab, Copenhagen*

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## The regulatory system in Denmark

### **Skinny-labelling/carve out**

- Generics are allowed to exclude indications still covered by patent when obtaining an MA under the abridged procedure

### **Indication on the prescription**

- In Denmark any prescription must include information about the indication

### **Substitution did not respect patent rights**

- The Danish Medicines Agency ("DKMA") decides which medicinal products can be substituted with each other - in substitution groups
- Patent rights were not taken into consideration
- The pharmacies are under an obligation to dispense the cheapest medicinal product in the same substitution group, unless the doctor has stated "No substitution" on the prescription, or the price difference is below certain limits

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## The Lyrica® case: Facts



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## The Lyrica® case: Facts

- Pfizer's second-medical use patent:  
***"Use of [pregabalin] or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating pain."***
- Pfizer marketed Lyrica® which contains pregabalin approved for three indications:
  - A. epilepsy,
  - B. generalized anxiety disorder and
  - C. neuropathic pain (still patent protection)
- The share of the sale of Lyrica® prescribed for the treatment of pain in Denmark amounted to approximately 50-60% of all sales of Lyrica®
- Krka marketed the generic product Pregabalin "Krka" approved and labelled only for the non-patent protected indications (a and b)

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## The Lyrica® case: The regulatory jeopardy



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## The Lyrica® case: The regulatory jeopardy

- Before generic entry, Pfizer contacted the DKMA to try to solve the problem that substitution between Lyrica® and generic pharmaceuticals could constitute patent infringement
- The DKMA asked the DKPTO for a memo about the scope of the second medical use patent in view of the substitution rules. The DKPTO found that:

***"When medicinal products are listed as substitutable and the pharmacist for that reason is obliged to hand over the least expensive of the medicinal products, then this will immediately lead directly to an infringement of the patent if the generic medicinal products are sold/put on the market for the use for the patented indication."***

- Despite the memo from the DKPTO, the DKMA - after consulting the Ministry - denied to alter the substitution rules at the time
- The DKMA decided to place Lyrica® and Pregabalin "Krka" in the same substitution group
- So, the pharmacies were obliged to dispense Pregabalin "Krka" even if the doctors had prescribed Lyrica® for pain

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## The Lyrica® case: Krka's efforts – to avoid use for pain

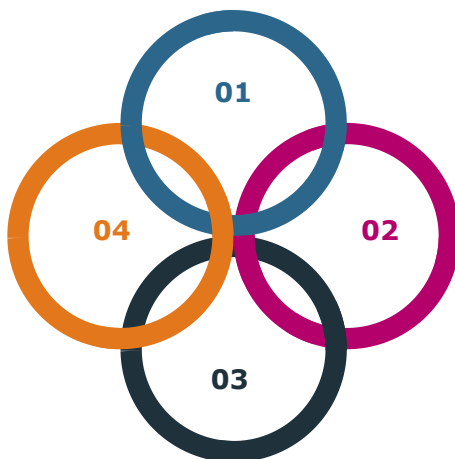


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## The Lyrica® case: Krka made efforts to avoid use for pain

**04**  
Krka contacted all websites that described the use of Pregabalin "Krka" and asked them to delete any text mentioning that Pregabalin "Krka" could be used for the treatment of pain

**03**  
Krka contacted the two Danish medicinal products wholesalers Nomeco A/S and Tjellesen Max Jenne A/S informing them of the matter, and provided them with a copy of the letter sent by Krka to all pharmacies in Denmark



**01**  
Krka contacted all general practitioners and all pharmacies in Denmark and encouraged them to abstain from prescribing, respectively from dispensing Pregabalin "Krka" for treatment of neuropathic pain

**02**  
Krka contacted the DKMA urging that a practical solution should be found as soon as possible to ensure harmonisation of the rules on patents and substitution

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## The Lyrica® case: Claims and main allegations



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## PI request against all 219 pharmacies in Denmark and Krka:

- Claims and infringement arguments against the pharmacies:
  - Claim for injunction against dispensing generic pregabalin for treatment of pain (many alternative claim formulations because of regulatory rules)
  - By dispensing Pregabalin "Krka" to patients for treatment of pain and placing a pain indication label on the product, the pharmacies commit a separate and direct patent infringement
- Claims and infringement arguments against Krka:
  - Claim for injunction against sale of Pregabalin "Krka" without ensuring that the product is not distributed and/or dispensed for the treatment of pain as long as the patent is in force
  - Claim for injunction against sale of Pregabalin "Krka" without providing express written instructions to the purchaser that the product must not be distributed and/or dispensed for the treatment of pain as long as the patent is in force
  - Contributory infringement

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## The Lyrica® case: Ruling



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## The Lyrica® case: Ruling

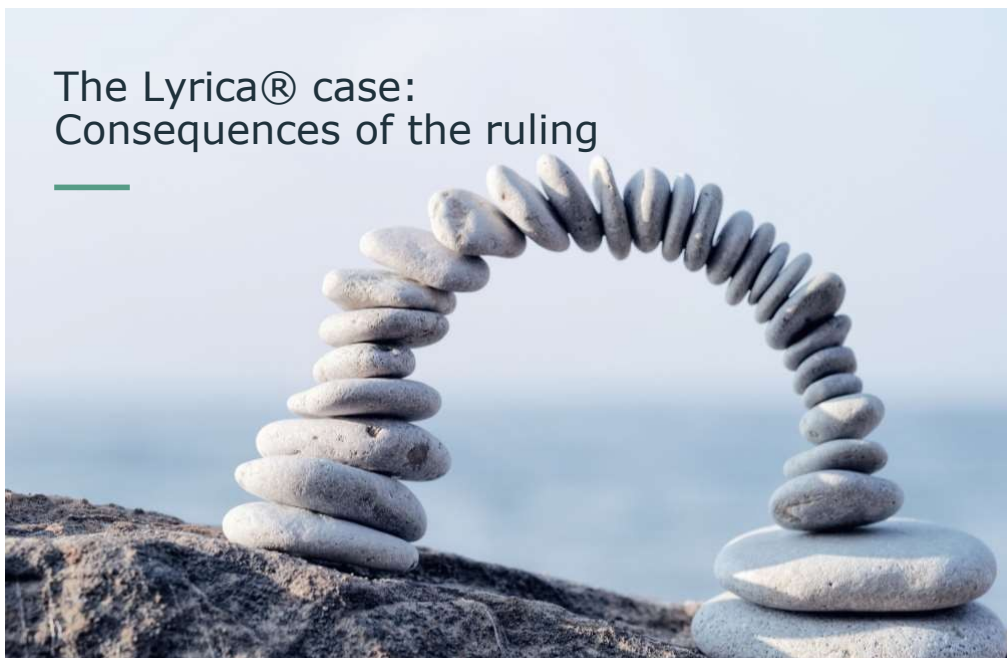
- The pharmacies were enjoined from dispensing Pregabalin "Krka" for the treatment of pain as long as Pfizer's patent is in force:

*"In consideration of the fact that the Patent in Suit is a second medical use patent with a Swiss-type claim **aimed at protecting the use of an already known substance for the treatment of a indication**, the court concurs that **the pharmacies' dispensing of Pregabalin "Krka" with a label stating that the medicinal product is intended for the patent protected treatment of the indication pain constitutes infringement of the Patent in Suit, see Section 3(1)(iii) of the Danish Patents Act.**"*

- The claim for an injunction against Krka was not allowed
  - The primary claim ("ensuring not dispensed for pain") not sufficiently clear to be enforced
  - Alternative claim already fulfilled (and PI was awarded against pharmacies)

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## The Lyrica® case: Consequences of the ruling



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## They changed the law

- Following the PI, the DKMA informed the doctors and pharmacies that the obligatory substitution between Lyrica ® and Pregabalin "Krka" was annulled
- Subsequently, the substitution rules were changed and now respect second medical use patent rights, so **"if a prescription for a medicinal product has been issued for the treatment of the patented indication, the pharmacy shall dispense the medicinal product with the patented indication"**
- The DKMA has asked patent holders to inform them of SMU patents and then notifies the pharmacies when a medicinal product has a patented indication
- The provision also applies to a situation where the doctor prescribes a generic product "off-label" under the doctor's freedom of prescription
- The provision does not apply to hospital pharmacies

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## Hospital Drugs



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## Hospital products sold through tenders

### The tender system in Denmark:

- Amgro is responsible for the procurement of 99% of all medicinal products used at the public hospitals. The procurement is organised through public tenders by Amgro
- Amgro does not organise tenders by indication. Instead, tenders are organised by active ingredient or therapy area, and Amgro does not regulate how the products are subsequently used by the hospitals
- The hospitals' use of medicinal products is regulated, inter alia, through the issue of various recommendations and guidelines from public advisory boards
- There are no specific rules that govern how Amgro/the regions/the hospitals must deal with second medical use patents
- The Ministry of Health in Denmark has stated that due to regulatory law, public bodies cannot recommend cross-label use when there is an approved drug for the relevant indication

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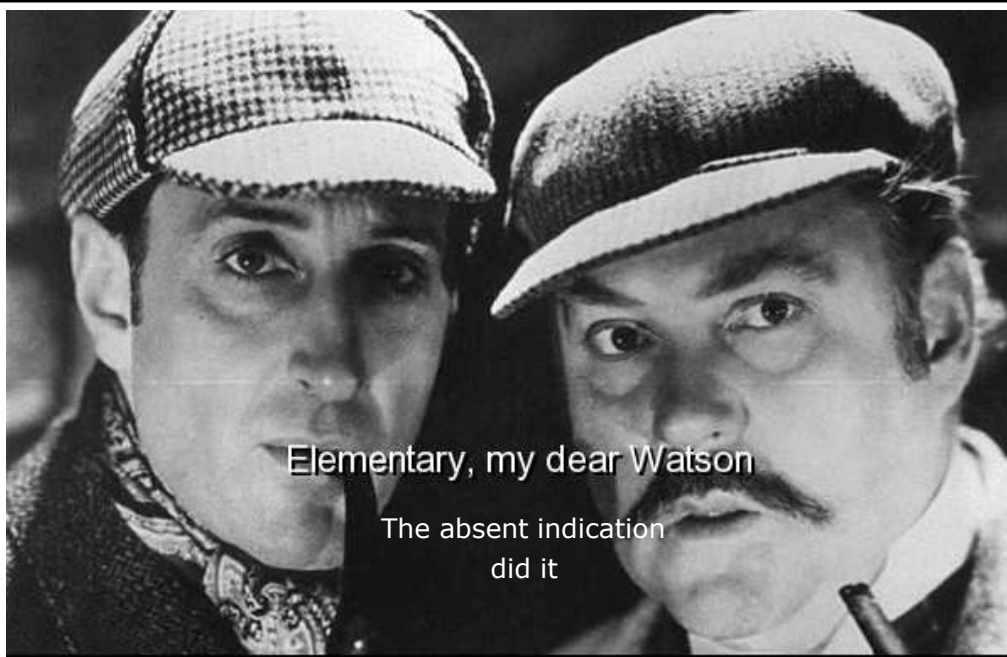
## Hospital products sold through tenders

### New model adopted by Amgro when SMU and drugs with skinny labels:

- Amgro enters into a number of parallel framework agreements
- One of the framework agreements is reserved for a medicinal product which is approved for the patented indication (full label product)
  - The winner of this framework agreement will normally be the original product (patentee), but can also be a full label generic product
- The tender conditions state that a certain share of sales is estimated to be used for the patented indication
- The hospitals are not obliged to buy the cheapest product if the product is not approved for the patented indication
- As there is no obligation as such for the doctors/hospitals not to use the drugs cross label, it is recommendable to follow up with the hospitals about this

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## Washington Second Medical Use Conference

**8/9 February 2018**

Panel F – 8 February 2018 – 11:50-12:50

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## Lyrica SMU Patent Infringement Cases in Selected Countries

- **USA:** US Court of Appeals for the Federal Circuit upheld injunction in February 2014
- **Australia:** 1<sup>st</sup> decision in May 2014 granted pi in appeal; latest decisions in February 2017 regarding PBS listing being no infringement
- **Germany:** 1<sup>st</sup> instance (LG Hamburg) granted pi in April 2015; patent invalidated in 2017
- **Denmark:** 1<sup>st</sup> instance decision in June 2015 (no infringement by Actavis, but by pharmacies)
- **Spain:** 1<sup>st</sup> instance decision in June 2015 (no pi granted); July 2016 pi granted on the grounds of indirect infringement in appeal
- **France:** 1<sup>st</sup> instance decisions in October 2015 and December 2016 (no infringement); July 2016 patent not invalid due to lack of sufficiency
- **Netherlands:** 1<sup>st</sup> instance decision in action against Dutch state in January 2016 (no infringement)
- **Sweden:** 1<sup>st</sup> instance decision regarding validity in August 2016
- **UK:** no pi in 1<sup>st</sup> instance and appeal in 2015 (invalidity suit pending in Supreme Court; hearing 12 to 15 February 2018)



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Lyrica® or PregabaHEXAL®

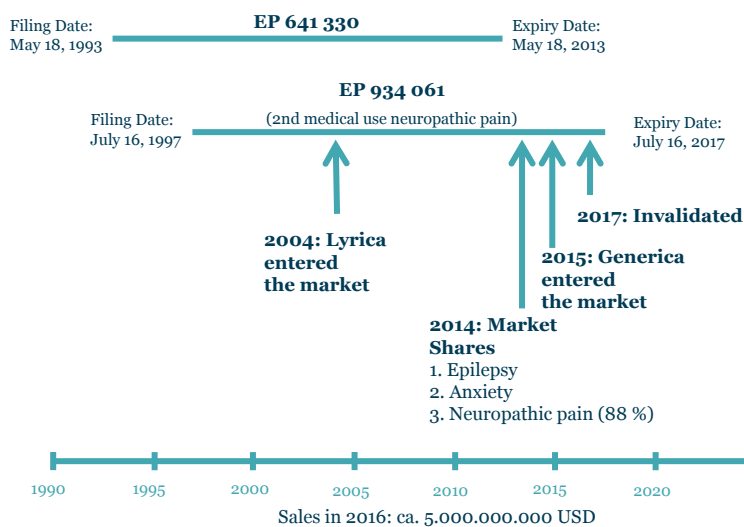
*Warner-Lambert vs. Hexal and KKH Decisions*

Panel F – 8 February

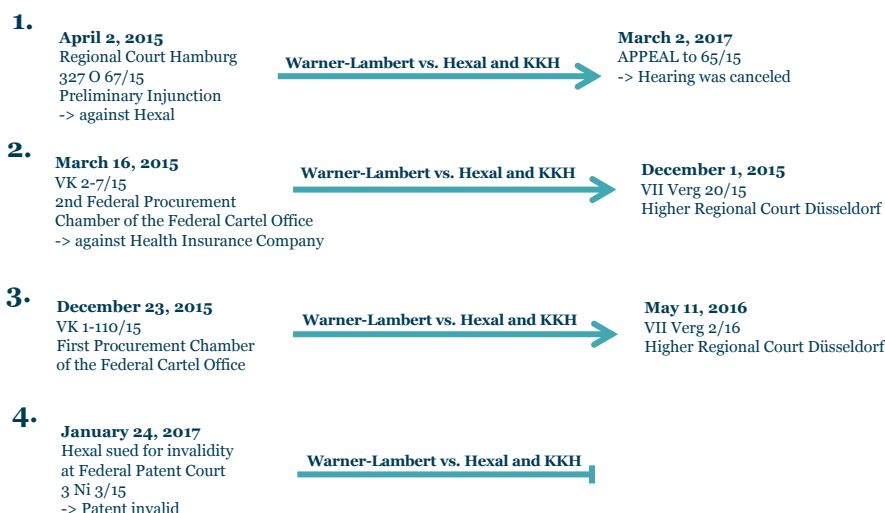
Dr. Ute Kilger

### Lyrica® or PregabaHEXAL®

#### *Warner-Lambert vs. Hexal and KKH Decisions*



## Legal procedure



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## Lyrice SMU Patent Case in UK

- 24 June and 12 September 2014: Revocation Claims by Mylan and Actavis
- 8 December 2014: Infringement suit by Warner-Lambert, including application for interim injunction
- **Interim Injunction Proceedings:**
  - 21 January 2015: Arnold J. dismissed application (no arguable infringement case; balance of justice favored refusal)
  - 28 May 2015 CoA dismissed Warner-Lambert's appeal (arguable infringement case, but balance of justice favored refusal and Arnold J. already ordered that NHS Commissioning Board should order that Lyrice must be prescribed for patented SMU)
- **Main Proceedings:**
  - 10 September 2015: Arnold J. partial revocation for insufficiency and no infringement; 25 November 2015: Arnold J. decided that amendments for claim 3 handed in by Warner-Lambert through conditional application is abuse of the process
  - 13 October 2016: CoA dismissed parties' appeals
  - 12 to 15 February 2018: oral hearing of Warner-Lambert's appeal against CoA decision regarding revocation of patent

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## Lessons learned from Lyrica SMU Patent Cases

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- Why are there so different decisions regarding infringement?
  - Direct infringement of SMU patents?
  - Indirect/ contributory infringement of SMU patents?
  - What could be expected from the manufacturer of the generic product?
- Are SMU patents – as such – more difficult to obtain and to defend?
- What changes are required for substitution rules for pharmacies?
- What changes are required in public tenders?
- What about doctor's freedom on prescription?
- Putting information regarding disease on prescription?