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# Nonrestorative Sleep – an approvable indication?


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# Agenda

- **Primary insomnia**
  - **Acute**
  - **Chronic**
  - **NRS**
- **Clinical trials**
  - **Population**
  - **Measurement tools**
  - **Primary and secondary endpoints**
- **Commentaries on the Guidance**

# EU: Approved Drugs for Primary Insomnia

- Only for short-term use
- Nothing yet for NRS
- Off-label:
  - Long-term use
  - Antidepressants
  - Antipsychotics

# History of the NfG „Insomnia

- First Guidance ECNP 1992
- Request for update 2009
  - Exchange between rapp. and experts
- Draft EWP and consultation 10/2009
- Deadline for comments 4/2010
- Transmission to CHMP for adoption 2/2011
- Came into effect 9/2011

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## Scientific guidelines

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**Important note on document formats:** All Microsoft Office documents submitted to the European Medicines Agency must be in a format compatible with MS Office 2003. Office 2007 and Office 2010 formats cannot currently be accepted.

The Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines, in consultation with the competent authorities of the EU Member States, to help applicants prepare marketing-authorisation applications for medicinal products for human use.

Guidelines are intended to provide a basis for practical harmonisation of the manner in which the EU Member States and the European Medicines Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community directives. They also help to ensure that applications for marketing authorisation are prepared in a manner that will be recognised as valid by the Agency.

For the assurance of quality of medicinal products, guidelines are complementary instruments to European Pharmacopoeia monographs and chapters.

**Compilation of European Commission and the European Medicines Agency scientific guidelines relating to medicinal products for human use**

This section of the website updates and replaces the previous Volume 3 of 'The rules governing medicinal products in the European Union' (EudraLex), published by the European Commission. It contains all currently valid guidelines originally published in Volume 3 and all currently valid guidelines published by the Agency since 1995, plus their subsequent revisions and supplements. As well as adopted guidelines, it also includes concept papers, draft guidelines and overviews of comments received during the consultation on draft versions.

- Blood and blood forming organs
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|---|---|---|---|---|---|
| Clinical investigation of medicinal products in the treatment of schizophrenia | Draft guideline<br>Concept paper | CHMP/40072/2010 | Released for consultation February 2011 | | Deadline for comments 31 August 2011 |
| Clinical investigation of medicinal products in the treatment of schizophrenia | Adopted guideline | CPMP/EWP/559/1995 | February 1998 | August 1998 | |
| Need for revision of note for guidance on clinical investigation of medicinal products in the treatment of depression with regard to treatment resistant depression | Concept paper | CHMP/EWP/484366/2009 | Released for consultation September 2009 | | Deadline for comments 31 December 2009 |
| Development of medicinal products for the treatment of alcohol dependence | Overview of comments<br>Adopted guideline<br>Draft guideline | CHMP/EWP/20097/2008 | March 2010 | September 2010 | |
| Clinical investigation of medicinal products for the treatment of attention-deficit/hyperactivity disorder (ADHD) | Overview of comments<br>Adopted guideline<br>Draft guideline<br>Concept paper | CHMP/EWP/431734/2008 | July 2010 | February 2011 | |
| New guideline on medicinal products for the treatment of insomnia | Overview of comments<br>Adopted guideline<br>Draft guideline<br>Concept paper | EMA/CHMP/16274/2009 | February 2011 | September 2011 | |
| Medicinal products for the treatment of insomnia | Adopted guideline | 3CC27A | | March 1992 | |

# Primary Insomnia (DSM IV-TR)

- – difficulties in initiating sleep;
- – disorders of maintaining sleep (frequent awakening);
- – premature awakening;
- – feeling of nonrestorative sleep,
- with subsequent impaired daytime functioning.

# Necessary to study

- The following clinical efficacy criteria should be evaluated as a minimum:
- – sleep onset latency;
- – sleep continuity;
- – sleep duration;
- – feeling of restorative sleep and quality of sleep;
- – subsequent daytime functioning in the natural setting.

# Based on „Subjectice Experience“

- **DSM-IV criteria are exclusively based on subjective experience**
  - Primary endpoint and labeling
  - *“efficacy will be based on clinical relevant improvements of subjective sleep parameters of the patients in their natural setting”*

- **Measures as Polysomnography are considered as pharmacodynamic measures and supportive**
  - Acceptable as primary endpoint in prrof of concept or dose-finding

# Possible Indication

- „is indicated for the treatment of insomnia, including difficulty falling asleep, nocturnal awakening or early awakening, in adults, usually for short term duration“

- If only one aspect is studied, e.g. NRS:
  - *In such cases the demonstrated effects should be based on a clear understanding of the underlying mechanism of action, should be robust and consistent and be supported by improvement in quality of day time functioning (mandatory as a co-primary endpoint)*

# Non Restorative Sleep / Sleep Disturbances Clinical Guideline: S3

- ***German Society for Sleep research and Sleep Medicine, published 2009***
- ***„Non restorative sleep" key issue of the guidance*** **as it is part of all insomnias, hypersomnias, circadian sleep abnormalities and sleep related apnoe syndromes**
- **Follows then usual classification system**
- **Evidenced based recommendations for diagnosis, treatment and further research needs**
- **Measurement of cognition and function**

# What‘s clinically meaningful, e.g. for NRS

- **Statistical Significance *and* Clinical Relevance**
- **Endpoints:**
  - **Co-Primary:** **- validated NRS questionnaire**
    **- validated functional improvement**
  - **Secondary:** **- global measures**
    **- polysomnography**
    **- others**
- **Difference between Baseline and Post-Treatment-Score**
- **Responder or Remitter Rates: ?**

# Conclusions from a Regulatory Point of View

- No approval for NRS yet
- Criteria to define a homogeneous population needed
- Validated measurement tools needed
- Subjective improvement should be supported by objective measures
- Subjective improvement should be supported by functional improvement, e.g. activities of daily living (co-primary)

- Scientific Advice at EMA or national competent authorities

# Thank You for Your Attention!