DIA Workshop: « Pharmacoeconomic and Quality of Life Labeling and Promotional Claims: A Global Update »

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Philadelphia, PA, USA

Role of Health-Related Quality of Life (HRQL) Outcomes in the European Drug Regulatory Process: Review of the EMEA documents (an update) »

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Objectives

- **To identify diseases or drugs in which a formal HRQOL assessment is recommended**
- **To identify measures and methods recommended**
- **To evaluate the reliability of recommendations across documents**
- ***To identify medicinal products registered with HRQL Labeling***

Overview

- ✓ The ERIQA project
- ✓ Background: European regulatory system
- ✓ Exploring the EMEA documents
- ✓ Examples
- ✓ Conclusion

ERIQA Project: Overview

Members
Academics
Ph. Industry
Reg. Authorities

1. To provide European Regulators with guidance on:
   - how to assess the quality of HRQL studies in RCTs,
   - how to evaluate the validity of HRQL claims
2. To convince European Regulators that HRQL is a relevant key outcome, *i.e. a credible criterion of evaluation*
3. To have them confident in the quality of HRQL outcomes

Contacts with regulators at each step

Phase I
Step 1: Review of existing guidelines
Step 2: Guidance document
Step 3: Pilots
Step 4: Harmonization meetings

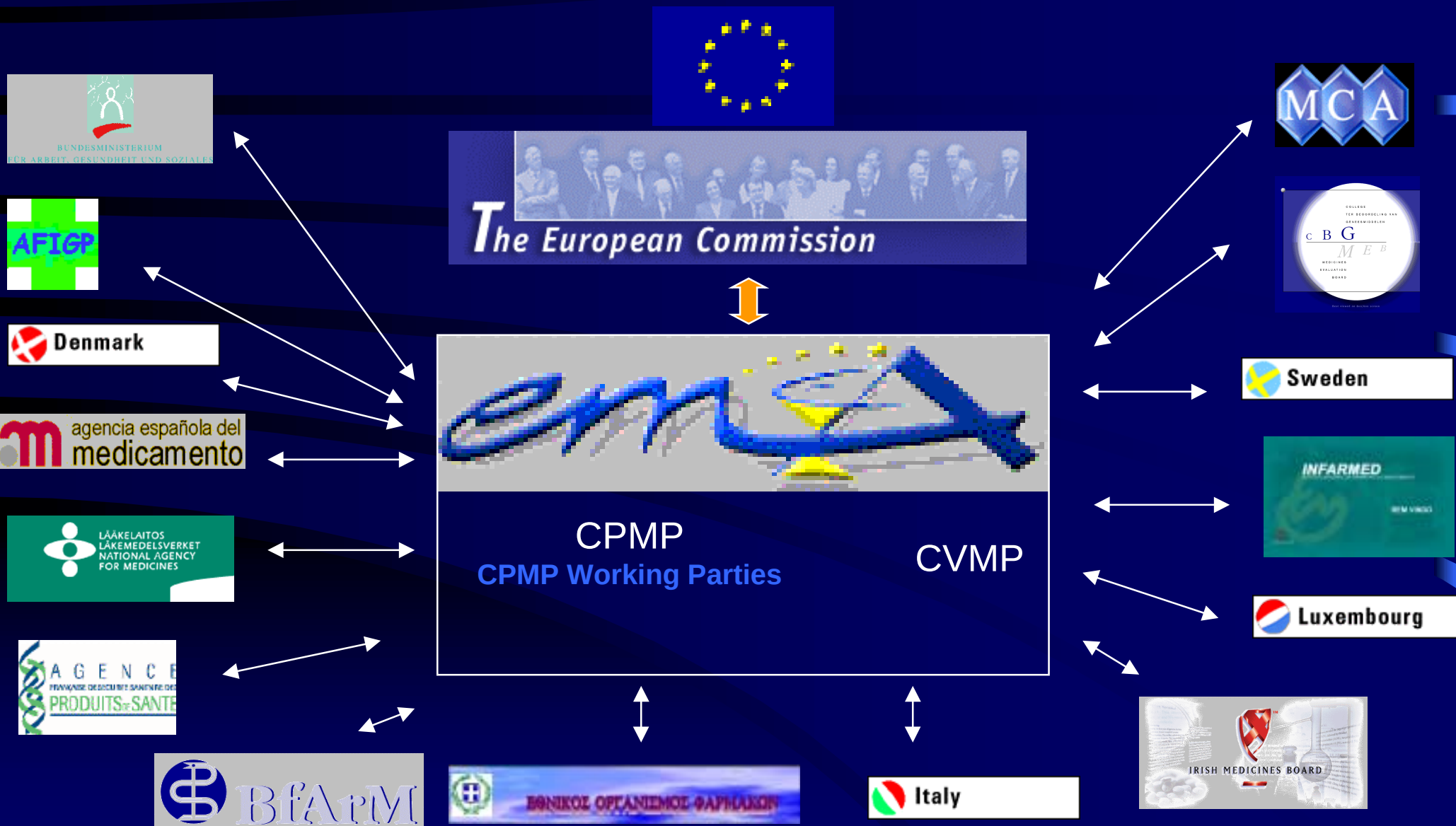
Phase II
Development of consensus guidelines in specific diseases

Collaboration with FDA, PhRMA HOC, ISOQOL, ISPOR

Results: Phase I - Step 1 Review

DATE	WHAT	WHO	PUBLICATION/ COMMUNICATION
08/1999	**Review of EMEA Guidelines**	Apolone,G. and Al	**PharmacoEconomics 2001; Vol 19, No. 2 : 187-195**
09/2000	**Update of 08/1999**	Acquadro,C. and Al (ERIQA Group)	**DIA, New Orleans, LA, USA** October 2-3, 2000
08/2001	• **Update of 09/2000** • **Review of Authorised Products**	Acquadro,C. Marquis,P. and Al (ERIQA Group)	**DIA, Philadelphia, PA, USA** October 29-30, 2001

EMEA: A Network Agency



The European Procedures for Authorisation

- **Centralized Procedure:**
  - Compulsory for biotech. medicinal products
  - Available for other innovative new products
  - Applications => EMEA, scientific evaluation in 210 days, opinion => European commission = single market authorization applying to the whole EU
- **Decentralized Procedure**
  - Applies to the majority of conventional medicinal products
  - Mutual recognition of national authorizations
  - EMEA arbitration, final decision by European commission

Country-specific Agencies

- **15 national agencies**
- **Control of RDP not homogeneous**
  - All → marketing authorization Pharmacovigilance
  - Most → information/advertising
  - Some → reimbursement
- **Examples:**
  - **France (AFSSAPS), Belgium (IGP):** total control
  - **Finland, Denmark, Germany**: only control of authorization, information
  - **Ireland:** only authorization

Material

- **EMEA Documents (July 31st, 2001) available on : www.eudra.org/emea.html**
  - **Efficacy Working Party Papers (Obj 1-3)**
  - **Medicinal Products with a Community Marketing Authorization (Obj 4)**

- **Key words:** Quality of Life, QoL

Efficacy Working Party Papers

- **Guidelines (Notes for Guidance - NG)**
  - Adopted
  - Drafts
- **Points to Consider**
- **Concepts Papers**

RESULTS: EWP Papers

EWP Papers	Total	+QOL Y2000	+QOL Y2001	Year 2001 compared to Year 2000
NG Adopted	24	9	8	→ 9 same conditions
NG Drafts	6	0	2	
Points to Consider	20	5	6	+1 (acute stroke)
Concept Papers	14	3	3	+2 (IBS, urinary incontinence) -2 (acute stroke, cardiac failure)
TOTAL	64	17	19	18 conditions (+2)

Identification of Conditions/Diseases

- CPMP/EWP NG: 9
  - Anti-Cancer Drugs in Man, Alzheimer's Disease
  - Stable Angina Pectoris, Antiarrythmics, Cardiac Failure,
  - Chronic Peripheral Arterial Occlusive Disease,
  - Multiple Sclerosis, Parkinson's Disease
  - Weight Control
- CPMP/EWP PC: 6
  - Acute Ischemic Stroke, Amyotrophic Lateral Sclerosis, COPD
  - Crohn’s Disease, Osteoarthritis, Rheumatoid Arthritis,
- CPMP/EWP CP: 3
  - Asthma, **IBS, Urinary Incontinence**

Identification of Measures: 3

cited as <u>examples</u> of measures that <u>might be used</u>

- **Chronic Cardiac Failure** (CPMP/EWP NG)
  - ➡ Minnesota Living with Heart Failure Questionnaire *(supportive end-point)*
- **Chronic Obstructive Pulmonary Disease** (CPMP/EWP PC)
  - ➡ Saint George's Respiratory Questionnaire *(primary symptomatic benefit end-point with FEV1)*
- **Crohn's Disease** (CPMP/EWP PC)
  - ➡ IBDQ *(secondary end-point)*

Recommendations/ NG: quotations

- **CPMP/EWP/235/95, Rev 1: Cardiac Failure**

  3.4. Quality of Life: *A broadly based assessment of the quality of life scales is recommended in Heart Failure studies because almost all components of the life quality may be influenced by an intervention for heart failure. Various QOL questionnaires have been used in the past and new ones devised. Unless these have been fully validated, evidence of efficacy derived from QoL questionnaires must be viewed as supportive only.*

  It is particularly important to consider whether (a) the scale is linear over the range of measurements, (b) is sensitive to the changes anticipated, (c) it is valid and useful to adjust results using the baseline scores, (d) there is any correlation between the score and the objective responses, (e) the observer and the patients should be blinded and (f) training of both the observer and the patient is necessary.

  Rating scales to assess QoL should also be considered and should have been validated beforehand in the context of the proposed trial and its aims.

  The Minnesota Living with Heart Failure Questionnaire is one of the many systems used in cardiac failure. *Translations of questionnaires used should also have been thoroughly validated beforehand.*

Recommendations/ NG: quotations

- **CPMP/EWP/561/98: Multiple Sclerosis**

  4.4. Quality of Life: *Few data are available on validation of specific instruments for QoL in patients suffering multiple sclerosis.* ***If a claim with respect to QoL in MS is considered, reliable and valid scales should be used.***

- **CPMP/EWP/563/95: Parkinson's Disease**

  4. Methods to assess efficacy: *the use of indirect efficacy variables as primary efficacy variable in pivotal studies, such as..[..]* ***quality of life.. is not recommended*** *unless the association between these variables and improvement in core symptoms or motor fluctuations or handicap has been proven*

Notes for Guidances

QOL is:

- Recommended as a potential efficacy criteria: **7**
- *And as secondary end-point: 3*
- Mentioned, but not to be recommended: **1** (Parkison)
- Only quoted (« qol of patients is impaired »): **1** (antiarrythmics)

CONCLUSION # 1

Compared to Y 2000

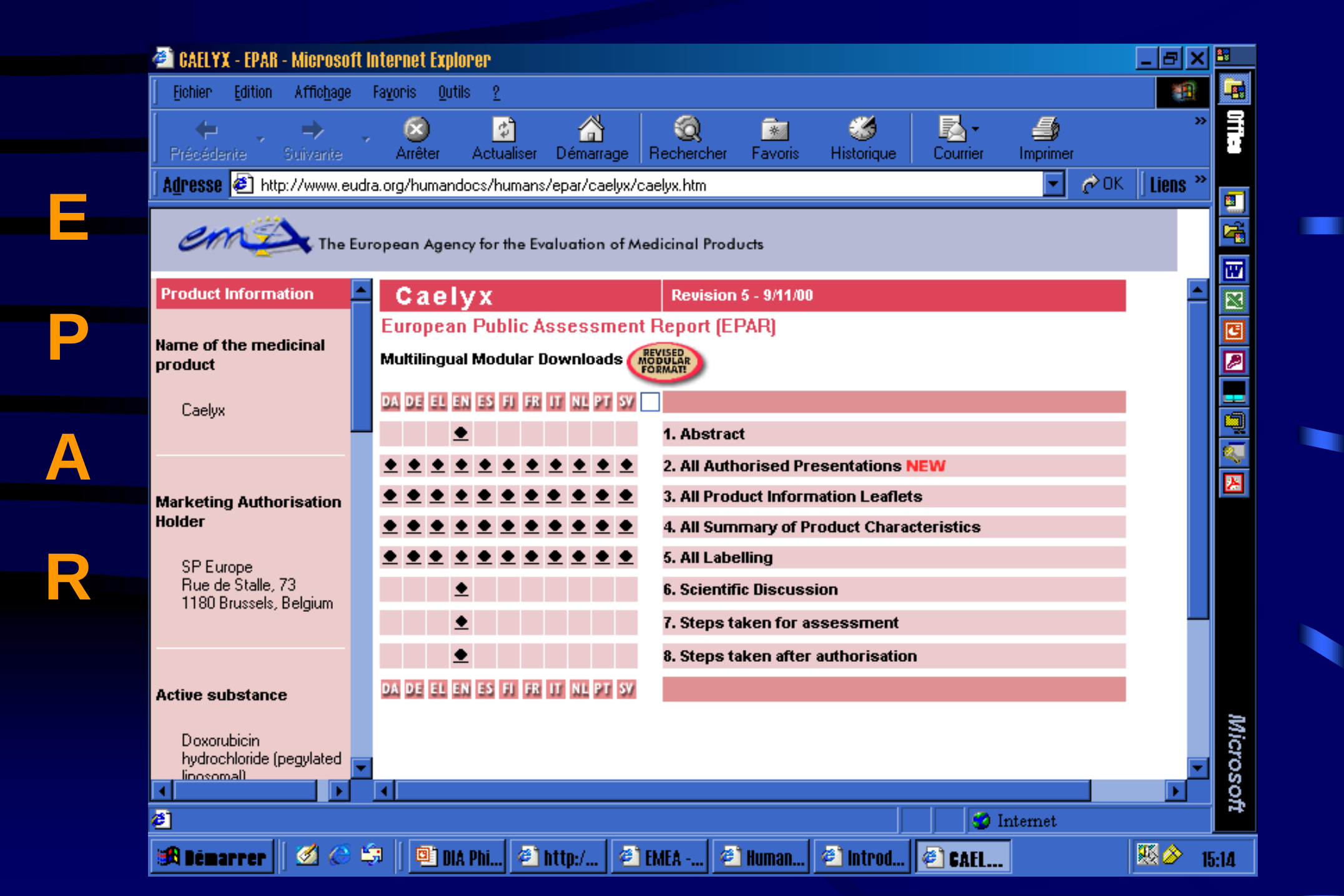
« NIHIL NOVI SUB SOLE »

Medicinal Products with a Community Marketing Authorisation

- "Authorised Human Products" list, *June 2001*
- European Public Assessment Reports: EPARs
  - Modular
  - Single (old) format

EPARs : definition

The European Public Assessment Report (EPAR) reflects the scientific conclusions reached by the Committee for Proprietary Medicinal Products (CPMP) at the end of the centralized evaluation process and provides a summary of the grounds for the CPMP Opinion in favor of granting a marketing authorization for a specific medicinal product. It is made available by the EMEA for information to the public, after deletion of commercially confidential information.


E
P
A
R
CAELYX - EPAR - Microsoft Internet Explorer
Fichier Edition Affichage Favoris Outils ?
Précédente Suivante Arrêter Actualiser Démarrage Rechercher Favoris Historique Courrier Imprimer
Adresse http://www.eudra.org/humandocs/humans/epar/caelyx/caelyx.htm
OK Liens
The European Agency for the Evaluation of Medicinal Products
Product Information
Name of the medicinal product
Caelyx
Marketing Authorisation Holder
SP Europe
Rue de Stalle, 73
1180 Brussels, Belgium
Active substance
Doxorubicin hydrochloride (pegylated liposomal)
Caelyx
Revision 5 - 9/11/00
European Public Assessment Report (EPAR)
Multilingual Modular Downloads
REVISED MODULAR FORMAT!
DA DE EL EN ES FI FR IT NL PT SV
1. Abstract
2. All Authorised Presentations NEW
3. All Product Information Leaflets
4. All Summary of Product Characteristics
5. All Labelling
6. Scientific Discussion
7. Steps taken for assessment
8. Steps taken after authorisation
Internet
Démarrer
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EMEA -...
Human...
Introd...
CAEL...
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Office
Microsoft

RESULTS

- 171 Products with Marketing Authorization (07/31/2001)
- 166 EPARs available, “explored” one by one with QoL, Quality of Life
- Focus on Abstract (A) and Scientific Discussion (SD)
- Assumptions:
  - A: Provides indication of future labeling & claim
  - SD: Provides back up evidence

RESULTS

- QoL assessed in 37 Products

- Only 2 products with mention of QoL both in abstract and scientific discussion:
  - **Caelyx** (Doxorubicin Hydrochloride)
  - **Thyrogen** (Thyrotropin alfa)

RESULTS

- Aerius (Desloratadine)
- Allex (Desloratadine)
- Azomyr (Desloratadine)
- Caelyx (Doxorubicin Hydrochloride)
- Cotronak (Ribavirin)
- Herceptin (Trastuzumab)
- Humalog (Insulin lispro)
- Hycamtin (Topotecan)
- IntronA (Interferon alfa-2b)

- Keppra (Levetiracetam)
- Lantus (Insulin glargine)
- Myocet (Doxorubicin)
- Neoclarityn (Desloratadine)
- Norvir (Ritonavir)
- NutropinAq (Somatropin)
- Olansek (Olanzapine)
- Optisulin (Insulin glargine)
- Opulis (Desloratadine)

RESULTS

- Panretin (Alitretinoin)
- Pegintron (Interferon alfa-2b)
- Rebetol (Ribavirin)
- Remicade (Infliximab)
- Stocrin (Efavirenz)
- Sustiva (Efavirenz)
- Taxotere (Docetaxel)
- Temodal (Temozolomide)
- Thyrogen (Thyrotropin alfa)
- Tikosyn (Dofetilide)
- Viagra (Sildenafil)
- Viracept (Nelfinavir)
- Viraferon(Interferon alfa-2b)
- ViraferonPeg (Interferon alfa-2b)
- Xeloda (Capecitabicine)
- Xenical (Orlistat)
- Zerit (Stavudine)
- Zyprexa (Olanzapine)
- Zyprexa Velotab (Olanzapine)

Examples

- Quality of life (EMEA)
- Discomfort (EMEA)
- Domain specific claim (Local)

Thyrogen
EPAR abstract

- **On 9 March 2000** the European Commission issued a Marketing Authorization valid throughout the European Union for the medicinal product Thyrogen, which contains Thyrotropin alfa. (…)
- The Marketing Autorisation Holder responsible for this medicinal product is Genzyme BV, Netherlands.
- The approved indication is **for use with radioiodine imaging together with serum thyroglobulin (Tg) testing undertaken for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on hormone suppression therapy (THST).**

Thyrogen
EPAR abstract *(cont'd)*

- Clinical trials investigated bioequivalence, pharmacokinetic properties, dose regimen, and the clinical safety and efficacy of Thyrogen. (…)

- … it was shown that there is a general absence of hypothyroid signs and symptoms **and better Quality of Life following Thyrogen.**

Thyrogen -- EPAR SD

Clinical Efficacy

- **Studies: TSH91-0601, TSH92-0601 and TSH95-0101**
- Similar design to evaluate the within-patient comparison pf ^{131} I imaging and Tg testing following Thyrogen stimulation while continuing THST (referred as Thyrogen phase) and after THST withdrawal (referred to as Hypothyroid phase). Whole body scan was performed 48-72 h after a diagnostic dose of 2-4mCi ^{131} I
- **Quality of Life assessment was made using the Profile of Mood State (POMS) and the SF-36.**

Thyrogen -- EPAR SD

Study: TSH92-0601

- Multi-centre open label, single arm safety and efficacy study
- 152 patients with well-differentiated thyroid cancer, treated with 2 injections of Thyrogen 24 hours apart.
- **Hypothyroid symptoms: for all the items of the POMS scale, significant paired differences ($p<0.05$) favoring Thyrogen was demonstrated**

Thyrogen -- EPAR SD

Study: TSH95-0101

- Multi-center open label, randomized 2-arm parallel study; Two dosing regimens evaluated.
- 254 patients enrolled, 229 treated with Thyrogen and randomized in either one of the two dosing regimens: 2 injections of 0,9 mg 24h apart (arm I) or 3 injections of 0,9mg 72h apart (arm II)
- **QOL data (SF-36) showed significant differences in favor of Thyrogen on PF, RP,BP,RE,MH, standardized Mental and Physical component scales)**

Thyrogen -- EPAR SD

Conclusions

- Number of studies small. However Thyroid carcinoma is an uncommon disease and maximum information has been gained
- The combination of Thyrogen-stimulated Tg and WBS is for the most part comparable to THST withdrawal in detecting Thyroid remnants and cancer
- There is a general absence of hypothyroid signs and symptoms and **better Quality of Life following Thyrogen**

Vaniqa: EPAR abstract

“On March 2001, the European Commission issued a Marketing Authorization valid throughout the European Union for the medicinal product Vaniqa which contains eflornithine. (…)The Marketing Authorization Holder responsible for this medicinal product is Bristol-Myers Squibb Pharma EEIG.

The approved indication is for facial hirsutism in women. (…) Patient self-assessments demonstrated a significantly reduced psychological discomfort with the condition, as measured by responses to a self assessment questionnaire. Vaniqa significantly reduced how bothered patients felt by their facial hair and by the time spent removing, treating, or concealing facial hair.”

VANIQA™ Eflornithine HCl Cream EMEA Labeling

Patient self-assessments demonstrated a significantly reduced psychological discomfort with the condition, as measured by responses to 6 questions on a visual analogue scale. **VANIQA™ significantly reduced how bothered patients felt by their facial hair and by the time spent removing, treating, or concealing facial hair**. Patient comfort in various social and work settings was also improved. Patient self-assessments were found to correlate with physician observations of efficacy. These patient-observable differences were seen 8 weeks after initiating treatment. The condition returned to pre-treatment levels within 8 weeks after discontinuation of treatment.

Peripheral Occlusive Arterial Disease

- Opinion leaders : QOL as an evaluation criteria
- EWP: QOL listed in the note for guidance
- Development and validation of a disease specific quest.
- RCT in two countries / QOL primary end-point
- Submission / questions / responses
- Claim obtained for 2 domains

Issues of the regulators

- Interpretation of the differences
  - Meaningfulness / clinical significance?
- Answers
  - Effect size
  - Meaningful change (response shift / SEM)
  - % Responders
  - NNT
  - Relative Benefit and Odd ratio

COMMENTS

- Positive messages
  - EWP does consider QOL as an evaluation criteria
  - Labeling obtained
- Concept of PRO operational
  - QOL / Discomfort / Domains specific

The work must go on!

- ERIQA has set up a database of existing labels
- Complex and time consuming task
- Further investigation needed
  - confirmation by EMEA or Pharma. Comp.
  - National level
  - Domain specific labels

Perspectives for the Future

ERIQA

- listed in EMEA EWP Interested Parties
- Invitation to review EWP Papers

CONCLUSION

- Opportunities for a better collaboration (Academics / Regulators / Industry)
- Not any more playing ...

  « the Good, the Bad, and the Ugly »
- Win / Win perspective
- Benefit to patients