INTRODUCTION TO PATIENT-REPORTED OUTCOMES (PROs) SUCH AS HEALTH-RELATED QUALITY OF LIFE, TREATMENT SATISFACTION, ETC

Stockholm

Thursday, March 4

13:15-14:45

Regulatory Issues

EMEA and the Regulatory Environment?

A Review of the EMEA Notes for Guidance

Catherine Acquadro, MD
Scientific Advisor,
Coordinator of the ERIQA Group,
Mapi Research Institute, France

EMEA Recommendations on PROs: A Review of the EMEA Notes for Guidance

Which Notes for Guidances ?

Efficacy? Safety? Quality ? ICH? etc.

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PRODUCT ALERT

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Monday, May 26, 2003

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Notes for Guidance (NfG)

- EMEA Documents available on:

  www.emea.eu.int/index/indexh1.htm

- Efficacy Working Party Notes for Guidance:
  - **Concept papers (CP)**
  - **Points to consider (PC)**
  - **Draft Guidelines (DG)**
  - **Approved Guidelines (AG)**

Today's Objective

- To identify diseases or drugs in which a formal Patient-Reported Outcomes (PROs) evaluation is recommended
- To identify recommended measures

Review of EWP NfG

Results (01/22/2004)

	# NfG	Mention of PROs	Incl. HRQOL
Concept Papers	14 (16)*	4 (4)	2 (2)
Points to consider	23 (22)	7 (7)	7 (7)
Draft Guidelines	10 (4)	5 (1)	3 (1)
Approved Guidelines	**38** (36)	**13** (12)	**12** (11)
TOTAL	**85** (78)	**29** (24)	**24** (21)

** Results of 05/27/2003*

Review of EWP NfG

29 Notes for Guidance including PRO evaluation

- **CVD:** Stable Angina Pectoris, Cardiac Failure, Chronic Peripheral Arterial Occlusive Disease
- **Gastro-Enterology**: Crohn's Disease, IBS
- **Neurology:** Acute Ischemic Stroke, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Migraine, Multiple Sclerosis, Neuropathic Pain Management, Nociceptive Pain*, Parkinson's Disease
- **Psychiatry**: General Anxiety Disorder, Panic Disorder, Obsessive Compulsive Disorder*, Social Anxiety Disorder*
- **Respiratory Diseases**: Asthma, COPD
- **Rheumatology**: Ankylosing spondylitis*, Osteoarthritis, Rheumatoid Arthritis
- **Others**: Anti-Cancer Drugs in Man, HIV, Psoriasis, Allergic Rhino-conjunctivitis*, Sepsis, Urinary Incontinence in Women, Weight Control

**HRQL not mentioned*

Review of EWP NfG

29 Notes for Guidance including PRO evaluation

- *Some examples:*
  - *Psoriasis*
  - *Rheumatoid Arthritis*
  - *IBS*
  - *COPD*
  - *Allergic Rhino-conjunctivitis*
  - *Multiple Sclerosis*

CPMP/EWP/2454/02: Psoriasis

CP

EWP Discussion Oct 2002 – Oct 2003

3. Discussion

It is suggested that the following topics are addressed in the guideline:

…[…]…

Choice of endpoints (PASI, BSA, clinical outcomes measures, quality of life)

Deadline for comments: May 2004

4. Methods to assess efficacy

4.1. Outcome measures

Both investigator's assessed outcome measures and patient's assessed outcome measures have been used in the overall evaluation of product efficacy. A reasonable consistency of response is expected with respect to the employed measures.

4.1.2. Patient's assessed outcome measures

These measures correspond both to efficacy endpoints evaluated by patients and to HRQL scales validated in dermatology:

- Patient's assessment of global improvement: the same as PGA, evaluated by the patient
- Patient's assessment of PASI (self-administered PASI – SAPASI)
- HRQL scales validated in dermatology:
  - General: Dermatology Life Quality Index (DLQI), Dermatology Quality of Life Scales (DQOLS), Skindex;
  - Specific for psoriasis: Psoriasis Disability Index, Psoriasis Life Stress Inventory (PLSI)

4.1.2. Patient's assessed outcome measures (cont'd)

Efficacy of a new drug evaluated by patient is important when the risk/benefit of each therapy is tended to be individualised and where even relatively limited extent of skin psoriasis may severely socially and psychologically disable the patient. It is of particular interest in diseases which do not cure or the existing drugs are only partially effective.

The assessment of HRQL scales specific for psoriasis may represent an added value for a new drug in comparative clinical trials, in addition to classical efficacy/safety measures. Patient-assessed drug efficacy may be a secondary or tertiary endpoint in pivotal clinical trial.

The validation of HRQL scales specific for psoriasis should be performed in separate trials. Ideally, trials assessing psoriasis-specific HRQL should be designed to assess patient's perspective in the evaluation of drug-effect in order to understand better the clinical significance of the benefit observed and to be sure that the administered treatment does not impact adversely on patient's QL. However these studies are difficult to perform as no consensus exists on their design.

EWP Discussion Feb 2001 – April 2002

5. Supportive evidence for efficacy

…[…]…

e) quality of life:

Of the above list only d) and e) are established as useful additional secondary endpoints.

Adoption by CPMP Dec 2003

3. Tools to measure efficacy (primary or secondary endpoints)

…[…]…

d) patient's global assessment of disease activity (VAS)

e) pain score (patient's assessment of pain, VAS, Likert Scale)

…[…]…

g) physical function (assessed by patient, e.g. HAQ, AIMS (function and quality of life)

Depending on the pharmacological rationale of the treatment studied, the primary efficacy measure(s) has/have to be chosen adequately. Results from the studies will have to be compatible with claim indications. Other measures may be acceptable if validated.

4. Supportive evidence for efficacy

…[…]…

d) emotional and social function (e.g. AIMS-1)

e) quality of life (RA-specific, e.g. AIMS, SF-36 or generic tests)

Of the above list ***only d) and e) are established as useful additional secondary endpoints (see 3.).***

EWP Discussion Nov 2000 - April 2002; CPMP adoption March 2003

5. Recommended primary/secondary efficacy endpoints

Primary: The patient's global assessment of symptoms and abdominal discomfort/pain should be used as the two primary endpoints. Statistically significant changes must be found in both parameters.

Secondary (supportive): choice of secondary efficacy variables should be justified by the applicant and should include variables such as bloating/distension, stool frequency and urgency, and quality of life parameters. Health-related quality of life must, however, be considered most important secondary endpoints

CPMP/EWP/562/98: COPD

PC

EWP Discussion Oct 1995 – Dec 19997; CPMP Approval Dec 1999

VI. Recommended Primary and secondary endpoints:

In the major efficacy studies of symptomatic benefit the primary endpoint should reflect the clinical benefit the applicant wishes to claim in the future SPC.

The Primary symptomatic benefit endpoint should be justified by referencing published data which support its validity; one example is the St George's Respiratory Questionnaire.

There are a number of secondary endpoints which may provide useful information. These measure different aspects of the disease but they should be justified by referencing published data which support their validity; examples include…..symptom scales, exacerbation rates and QoL assessment.

Which are chosen will depend upon the claims being made in the SPC. Care should be taken with respect to statistical multiplicity if secondary endpoints become the basis for specific claims.

II. Methods to assess efficacy

Choice of endpoints

Symptomatic relief: Primary efficacy analyses

In allergic rhino-conjunctivitis trials primary measures of efficacy are patient self-rated symtoms scores. Symptom scores should be collected at baseline and daily over the course of the trial. Baseline time period should be defined. It is recommended to score the symptoms at last daily. The patient should report on his status and symptoms over the previous period of 24 hours. For SAR, scoring in the evening time is recommended while in PAR, scoring on awakening might be more appropriate.

There are no standardised and generally accepted scales for scoring nasal and eye symptoms/signs in SAR/PAR studies.The symptom scale should be clearly defined, validated, and easily understood by both patients and physicians.

II. Methods to assess efficacy

Choice of endpoints

Symptomatic relief: Primary efficacy analyses (cont'd)

…[…]…The scores should be presented in a main symptom sum-score, nasal symptom sum-score and/or eye symptom sum-score. An appropriate primary efficacy end-point is the change from baseline in the total patient symptom score during the entire double-blind period…[…]…The applicant should provide a value for a clinically meaningful change in the primary efficacy endpoint and the basis for this value. A merely significant difference of xx points on a scale might not be sufficient. An analysis in term of responder (e.g. patients with a 50% reduction in symptom score) might be helpful.

For an efficacy claim in allergic rhino-conjunctivitis, efficacy for the nasal and eye symptom-score should be proven separately…[…]…

II. Methods to assess efficacy

Choice of endpoints (cont'd)

Symptomatic relief: Secondary efficacy analyses

These may include the individual patient-rated symptoms, symptom-free days, physician-rated symptoms, clinical global improvement (CGI), predefined area under curve (AUC). Rescue medication should form part of secondary efficacy analyses. (Secondary efficacy analyses may be used to indicate time to maximal effect, and onset of action).

Preventive medication: Primary measures of efficacy

Days of freedom from symptoms or in the event of symptoms occuring the number of days of no or minimal symptoms as predefined.

Preventive medication: Secondary efficacy analyses

These may include the individual patient-rated symptoms, use of rescue medication, symptom-free days, physician-rated symptoms, CGI, predefined AUC. These may be used to indicate time to maximal effect, and onset of action.

CPMP/EWP/561/98: Multiple Sclerosis

AG

EWP Discussion July 1998 – June 1999; CPMP adoption July 2001

4. Methods to assess efficacy

...[...]...

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.

Review of EWP NfG

PROs:

- **Recommended as primary end-point: 9 NfG**

  Allergic Rhino-Conjunctivitis, COPD, General Anxiety Disorder, IBS, Migraine, Nociceptive pain, Osteoarthritis, Psoriasis, RA, Urinary Incontinence in women

  ➔PROs = Symptoms, pain, discomfort, never HRQL

- **Also Recommended as a secondary end-point: 18 NfG**

  ALS, Asthma, Cancer, CHF, COPD, Crohn, General Anxiety Disorder, IBS, MS, OCD, Osteoarthitis, Panic Disorder, PAOD, Psoriasis, RA, Stable Angina, Urinary Incontinence, Weight Control

Review of EWP NfG

PROs:

- **Recommended as a potential efficacy endpoint**:

  4 NfG: Ankylosing spondylitis, Neuropathic Pain Management, Sepsis, Social Anxiety Disorder (concept papers)

- **Useful in safety: 1 NfG** – HIV
- **Mentioned but not recommended: 2 NfG -** Alzheimer Disease, Parkinson

Development of HRQL scale encouraged in:

1 NfG - Stroke

Review of EWP NfG

Examples of PRO Questionnaires which might be used

- AIMS, DLQI, DQLS, HAQ, HAM-A
- IBDQ, Liebowitz Social Anxiety Scale
- Minnesota Living with Heart Failure
- *Patient self-rated symptoms scales*
- PLSI, Psoriasis Disability Index
- St Georges Respiratory Questionnaire
- Sheenan Disability Scale, Skindex, Womac
- *HRQL « Generic » instruments, SF-36*
- *HRQL Disease specific questionnaires*

Do EMEA guidelines recommend the assessment of PROs in clinical trials ?

YES!

But…the term PRO is not yet accepted or recognised by the EWP

Conclusion

- **Recognition of:**
  - The value of the Patient's perspective in the evaluation of medicines
  - HRQL as a valuable endpoint (mainly secondary)
- **Quality of guidelines**
  - Need to improve consistency between NG
  - Need to update obsolete guidelines
- **Next Step**: Devt of a Position Paper

Useful Information

Websites

- EUROPA – The Web Service of the European Commission: http://europa.eu.int
- Pharmaceuticals and Cosmetics Unit (European Commission – Enterprise Directorate-General): http://pharmacos.eudra.org
- EMEA:http://www.emea.eu.int/
- EU Agencies Web Site: http://heads.medagencies.org/
- ISPO – The EC Information Society Project Office: http://www.ispo.cec.be/
- CORDIS – Community Research and Development Information Service: http://www.cordis.lu/
- EUR-OP – The EC's Official Publications Office: http://eur-op.eu.int/

Appendix

All NfG quoting PROs*

by type

and as listed on the EMEA Website (01/20/2004)

Focus on HRQL

Appendix

Concept Papers: 4

3. Discussion

It is suggested that the following topics are to be addressed:

…[…]…

<u>Study design</u>

…[…]…

Primary and secondary endpoints (e.g. pain reduction, functional and social performance, quality of life)

I. Introduction

…[…]…

In conclusion, SAD is associated with severe psychosocial impairment and significant negative effects on social functioning and quality of life.

III. Discussion

Scales chosen in pivotal clinical clinical trials should be sensitive, validated, internationally recognised and have demonstrate the ability to separate active treatment from placebo reliably. Different scales have been utilized for quantifying the severity of SAD. The Liebowitz Social Anxiety Scale (LSAS) had been applied most widely. Other scales as the « Brief Social Phobia Scale », the « Social Avoidance and Anxiety Inventory », the « Brief Standard Self-rating for Phobic Patients » and the « Social Avoidance and Distress Scale » have also confirmed useful in studies, however the LSAS is seen as the standard instrument.

III. Discussion

The main controversial topics to be addressed in the guidance are:

1. Differences and definition of a « symptom relief » claim, and claims on « symptom modifying » or « disease controlling ».

2. Selection of patients

3.Main efficacy variables according to the possible therapeutic claims and different domains of the disease. There are several available scales either to measure changes in specific domains or as composite indexes.

…[…]…

III. Discussion

The main topics to be addressed in the guidance document are:

…[…]…

3. Questions related to study design as:

…[…]…

- Outcome measures (mortality, morbidity outcomes, quality of life)

Appendix

Points to Consider: 7

II. Recommended primary/secondary efficacy endpoints

a) Symptom modifying drugs

Pain attributable to the target joint is recommended as primary endpoint. Functional disability is an important additional primary endpoint.

Pain should be measured by self-assessment with validated methods, such as visual analogue or Likert scales.

Functional disability

A disease-specific and joint specific instrument such as the **WOMAC**…[…]…is recommended.

Secondary endpoints include:

Global rating, Flares, Physical signs including range of motion, Quality of Life, Consumption of medications for pain relief

VI. Recommended Primary and secondary endpoints:

In the major efficacy studies of symptomatic benefit the primary endpoint should reflect the clinical benefit the applicant wishes to claim in the future SPC.

The Primary symptomatic benefit endpoint should be justified by referencing published data which support its validity; one example is the St George's Respiratory Questionnaire.

There are a number of secondary endpoints which may provide useful information. These measure different aspects of the disease but they should be justified by referencing published data which support their validity; examples include…..symptom scales, exacerbation rates and QoL assessment.

Which are chosen will depend upon the claims being made in the SPC. Care should be taken with respect to statistical multiplicity if secondary endpoints become the basis for specific claims.

VIII. Methods of Efficacy Variables Measurement

VIII.4. Function Tests (Assessment of Disability)

Efficacy variables should include functional tests of disability. These maybe rating scales or functional scales. Rating scales should be validated for ALS. Examples include the ALS Functional Rating scale, the Baylor ALS Rating Scale.

VIII.5. Assessment of Quality of Life:

Measurement of QoL is a valuable and independent measure of therapeutic efficacy, which may be applied as a secondary end-point in ALS trials.

Use as a primary endpoint is not recommended.

Quality of Life scales specific to ALS have not been developed, and the use of a well-known general Quality of Life scale as an additional secondary end-point should be validated.

2.2. Management of Crohn's disease and potential claims:

Other end-points such as fistula healing, steroid sparing, treatment of abscess, treatment of obstruction and improvement in quality of life can be subsumed as response variables or outcomes measures of either the treatment of active disease or maintenance of remission. Unless otherwise justified, they should not be mentioned in the indication.

EFFICACY

2.2.1 Treatment of active disease/Induction of remission

2.2.1.3 Response variables

Secondary endpoints may include:

Validated QOL measurement, e.g. IBDQ

3. Methods to assess efficacy

Assessment scales for the measurement of stroke-related impairment, disability and handicap include neurological deficit scales, functional and global outcome scales as well as health-related quality of life scales (although the latter have not been developed specifically for stroke and have yet to be validated)

3.4. Health-related Quality of Life scales

At present, QOL scales are not among the primarily focused end-points in stroke. If these scales are used, they should be validated for stroke. Development of validated scales is encouraged for future trials.

In case QOL scales are used as additional evidence, special attention should be paid to possible confounding factors such as post-stroke depression or change in the environment that might interfere with the specific treatment effects.

5. Recommended primary/secondary efficacy endpoints

Primary: The patient's global assessment of symptoms and abdominal discomfort/pain should be used as the two primary endpoints. Statistically significant changes must be found in both parameters.

Secondary (supportive): choice of secondary efficacy variables should be justified by the applicant and should include variables such as bloating/distension, stool frequency and urgency, and quality of life parameters. Health-related quality of life must, however, be considered most important secondary endpoints

CPMP/EWP/556/951: Rheumatoid Arthritis

PC

3. Tools to measure efficacy (primary or secondary endpoints)

…[…]…

d) patient's global assessment of disease activity (VAS)

e) pain score (patient's assessment of pain, VAS, Likert Scale)

…[…]…

g) physical function (assessed by patient, e.g. HAQ, AIMS (function and quality of life)

Depending on the pharmacological rationale of the treatment studied, the primary efficacy measure(s) has/have to be chosen adequately. Results from the studies will have to be compatible with claim indications. Other measures may be acceptable if validated.

4. Supportive evidence for efficacy

…[…]…

d) emotional and social function (e.g. AIMS-1)

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Of the above list ***only d) and e) are established as useful additional secondary endpoints (see 3.).***

Appendix

Draft Guidelines: 5

II. Methods to assess efficacy

Choice of endpoints

Symptomatic relief: Primary efficacy analyses

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II. Methods to assess efficacy

Choice of endpoints

Symptomatic relief: Primary efficacy analyses (cont'd)

…[…]…The scores should be presented in a main symptom sum-score, nasal symptom sum-score and/or eye symptom sum-score. An appropriate primary efficacy end-point is the change from baseline in the total patient symptom score during the entire double-blind period…[…]…The applicant should provide a value for a clinically meaningful change in the primary efficacy endpoint and the basis for this value. A merely significant difference of xx points on a scale might not be sufficient. An analysis in term of responder (e.g. patients with a 50% reduction in symptom score) might be helpful.

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II. Methods to assess efficacy

Choice of endpoints (cont'd)

Symptomatic relief: Secondary efficacy analyses

These may include the individual patient-rated symptoms, symptom-free days, physician-rated symptoms, clinical global improvement (CGI), predefined area under curve (AUC). Rescue medication should form part of secondary efficacy analyses. (Secondary efficacy analyses may be used to indicate time to maximal effect, and onset of action).

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Preventive medication: Secondary efficacy analyses

These may include the individual patient-rated symptoms, use of rescue medication, symptom-free days, physician-rated symptoms, CGI, predefined AUC. These may be used to indicate time to maximal effect, and onset of action.

II. Methods to assess efficacy

Primary efficacy endpoints in confirmatory trials

Efficacy will assessed by rating scales. The choice of rating scales should be justified from the test quality criteria (reliability, validity) and the sensitivity for changes should be known. For the assessment of improvement specifically developed rating scales are necessary.

The Hamilton anxiety rating scale (HAM-A) is a widely used, though not optimal scale. The total scale can be used as primary endpoint, whereas the HAM-A psychic anxiety factor may be useful as a secondary endpoint. Other scales, such as Pittsburgh scale, could be used provided that they are validated and that HAM-A is also measured for internal validation.

Improvement of symptomatology should be documented as a difference between baseline and post-treatment score, but should also be expressed as the proportion of responders and/or remission. Responders are defined as patients with a clinically relevant reduction from baseline on the primary outcome scale.

II. Methods to assess efficacy

Primary efficacy endpoints in confirmatory trials (cont'd)

Remission is defined as a condition where no or only few signs of illness remain.

The cut-off on validated rating scale has to be defined in the protocol and should be justified (for response and remission). In advance and during the study investigators should be trained to become and stay interreliable.

Seconday efficacy endpoints in confirmatory trials

Global assessment (e.g. item 1 and 2 on the Clinical Global Impression Scale of Global Improvement) may be used as secondary endpoint.

Other supportive efficacy criteria

Changes from Baseline for HAM-A psychic and somatic anxiety factors , CGI Severity of Illness, QoL may be used when validated for the patient population, Sheenan Disability Scale.

3. Methods to assess efficacy

…[…]…

3.3. Other supportive efficacy criteria

- Changes from baseline in the Sheehan Disability Scale
- CGI Severity of Illness
- QoL may be used when validated for the patient population

3. Methods to assess efficacy

3.1. Definition of the secondary parameters

As stated above, when the Y-BOCS is used as primary endpoint, the NIMH-OC should be used as secondary endpoint.

Because OCD significantly impacts on global social functioning (relationships, work, etc.), it may be useful to measure social and occupational function on a global scale that is independent of the disorder-specific scales. This may provide additional information on the clinical relevance of the treatment. The scales to be used should be validated and the choice should be motivated. Examples of global scales are the Global Clinical Impression Sacle (investigator rating scale) and the Sheenan disability scale (self rating scale).

Deadline for comments: May 2004

4. Methods to assess efficacy

4.1. Outcome measures

Both investigator's assessed outcome measures and patient's assessed outcome measures have been used in the overall evaluation of product efficacy. A reasonable consistency of response is expected with respect to the employed measures.

4.1.2. Patient's assessed outcome measures

These measures correspond both to efficacy endpoints evaluated by patients and to HRQL scales validated in dermatology:

- Patient's assessment of global improvement: the same as PGA, evaluated by the patient
- Patient's assessment of PASI (self-administered PASI – SAPASI)
- HRQL scales validated in dermatology:
  - General: Dermatology Life Quality Index (DLQI), Dermatology Quality of Life Scales (DQOLS), Skindex;
  - Specific for psoriasis: Psoriasis Disability Index, Psoriasis Life Stress Inventory (PLSI)

4.1.2. Patient's assessed outcome measures (cont'd)

Efficacy of a new drug evaluated by patient is important when the risk/benefit of each therapy is tended to be individualised and where even relatively limited extent of skin psoriasis may severely socially and psychologically disable the patient. It is of particular interest in diseases which do not cure or the existing drugs are only partially effective.

The assessment of HRQL scales specific for psoriasis may represent an added value for a new drug in comparative clinical trials, in addition to classical efficacy/safety measures. Patient-assessed drug efficacy may be a secondary or tertiary endpoint in pivotal clinical trial.

The validation of HRQL scales specific for psoriasis should be performed in separate trials. Ideally, trials assessing psoriasis-specific HRQL should be designed to assess patient's perspective in the evaluation of drug-effect in order to understand better the clinical significance of the benefit observed and to be sure that the administered treatment does not impact adversely on patient's QL. However these studies are difficult to perform as no consensus exists on their design.

Appendix

Adopted Guidelines: 13

CPMP/EWP/234/95: Stable Angina Pectoris

AG

2. Criteria of Efficacy

2.2. Anginal pain: Frequency, intensity and duration of anginal pain… should be documented. It is highly relevant as a secondary end-point.

2.3. Quality of life: *QoL measurement can provide valuable information about the effect of therapy on the general health status*

3. Methods to assess efficacy

3.2. Anginal Pain: The patient's experience of anginal pain should be recorded in a patient diary. The daily frequency of anginal pain should whenever possible be registered by patients using available log books.

3.3. Quality of life: *A QoL assessment may be considered, provided the questionnaire is validated in the context of the proposed target group.*

2. Study design and methods

2.2 Choice of tools

...[...]...

2.2.5. Quality of Life:

Although QOL is an important dimension of the consequences of diseases the lack of validation of its assessment in AD does not allow specific recommendations to be made as yet. When adequate instruments to assess this dimension in patients and their care givers become available, QOL assessment may be justified in AD trials

2. Assessment of Efficacy Criteria

2.2. Secondary (supportive) Efficacy Endpoints:

Choice of secondary variables should be justified by the applicant and could include variables such as quality of life parameters, biochemical parameters of lipid and glucose metabolism as well as blood pressure, cardiac function and sleep apnoea episodes.

4. Methods to assess efficacy

The use of indirect efficacy variables as primary efficacy variable in pivotal studies, such as an improvement in the clinical global impression, quality of life or L-dopa+ savings is not recommended unless the association between these variables and improvement in core symptoms or motor fluctuations or handicap has been proven.

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

AG

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.*

4. Methods to assess efficacy

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.

3.1.2. & 3.2.4. Other clinical parameters: *In long-term therapeutic studies with an appropriate sample size of patients, the assessment of QoL should also be performed by using general or disease specific questionnaires. However, at present not fully validated scales are available for this purpose.*

CPMP/EWP/714/98 rev 1: PAOD

AG

3.3, 4.3, 5.3 Criteria of Efficacy

3.3.2, 4.3.2, 5.3.2 Secondary end-points

3.3.2.4, 4.3.2.4, 5.3.2.5 Quality of Life

In trials with adequate sample size an assessment of Quality of life may be performed by using properly validated general and disease specific questionnaires.

8. Recommended Primary and Secondary end-points

8.4. Selection of Secondary end-points

…a number of secondary endpoints may provide useful information. These measure different aspects of the condition and they should be justified by referencing published data that support their validity. Examples in chronic asthma include symptom scores, use of rescue medication, nocturnal symptoms, exercise tolerance, exacerbation rates and quality of life.

4. Clinical Outcome Measures

4.2. Quantification of symptoms

4.2.3. Quality of Life

Disease specific and generic instruments for measuring HRQL can be used in trials of products for urinary incontinence. The instruments used should be properly validated.

A clinically relevant change in pre-specified domains (dimensions) of QOL should be defined and justified in the protocol of the study. HRQL data should be considered an extension of an evaluation of efficacy, which can provide meaningful information to the prescriber and the patient. HRQL data can, however, never be the sole basis for efficacy claims. HRQL data usually do not contribute data to be included in section 4.1 [Subjective outcomes measures].

Indication of the SPC, may, if clinically relevant changes have been found, be included in other parts of the SPC (e.g. section 5.1 Pharmacodynamics)

3. General aspects of study design

3.2. Measures of treatment outcome and supplementary investigation

3.2.7. Safety

The use of justified Quality of Life Instruments in long term controlled and preferably double-blind studies may provide additional information of principal importance in the assessment of benefit risk, given the impact of poor tolerability on compliance and psychosocial well-being.

4. Phase III Trials

4.1 Objectives and background

4.12. To study the effects of a new agent. Appropriate end-points of assessment include: progression-free/recurrence-free/relapse-free survival, overall survival, response rate, *symptom control/quality of life*

4.5 Evaluation of Efficacy

4.5.4. Symptom control and quality of life: *The choice of scales should be justified and the validity of the scale for the specific study population and its reliability should be documented. Cultural aspects should be taken into account, especially in the case of multinational studies.*

5. Requirements for authorisation

5.3.2.Quality of Life Studies: *QOL studies may be used to support symptom control data provided that established quality of life questionnaires (including for example level of hospitalisation) are used, which are relevant to the study population treated.*

II. Method to assess efficacy

Acute migraine attack trials

…[…]… HRQL measures are not fully established in migraine, and their use is optional as one of the secondary endpoint.

Migraine Prophylaxis trials

Secondary endpoints might be:

…[…]… The use of HRQL measures and Disability-adjusted life years (DALYs) is not established, and they should not be used until fully clinically validated