



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 18 December 2002
CPMP/EWP/18/01 final

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF
MEDICINAL PRODUCTS FOR THE TREATMENT OF URINARY
INCONTINENCE**

DISCUSSION IN THE EFFICACY WORKING PARTY	February 2001 / October 2001
TRANSMISSION TO CPMP	November 2001
RELEASE FOR CONSULTATION	November 2001
DEADLINE FOR COMMENTS	May 2002
DISCUSSION IN THE EFFICACY WORKING PARTY	September/October 2002
TRANSMISSION TO CPMP	December 2002
ADOPTION BY CPMP	December 2002
DATE FOR COMING INTO OPERATION	June 2003

NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF URINARY INCONTINENCE

1. INTRODUCTION/BACKGROUND

Urinary incontinence among women is a prevalent condition, with a substantial impact on well being. Prevalence rates vary between 10 and 60% depending on the definition of incontinence and the age of the women. The prevalence of daily incontinence in several studies has been found to be 4-6%.

This note for guidance is intended to give advice to sponsors on the clinical development of medicinal products to be used for female urinary incontinence, excluding incontinence related to local pathologies, such as infective, neoplastic, fistulous, metabolic or hormonal processes. Although not specifically discussed in this note for guidance much of the guidance can be used in the development of drugs for male incontinence or neurogenic incontinence.

This document should be read in conjunction with the Directive 75/318/EEC, as amended, and all other relevant current and future EU and ICH guidelines.

2. DEFINITIONS AND DIAGNOSIS

The two main types of incontinence encountered in women are stress (effort) and urge incontinence. The term mixed incontinence denotes the concomitant appearance of stress and urge incontinence.

Incontinence may be diagnosed at three different levels;

- as a symptom voiced by the patient
- as a sign observed by the physician using simple means to verify the symptom
- as a condition, defined by the presence of urodynamic observations associated with symptoms or signs

2.1 Stress incontinence

Symptom: Stress urinary incontinence is the complaint of involuntary leakage on effort or exertion, or on sneezing and coughing. (New ICS definition)

Sign: The investigator observes urinary leakage from the urethral meatus synchronous with e.g. coughing or straining.

Condition: Urinary leakage occurs simultaneously with a cough without concomitant increase in detrusor pressure (this requires the simultaneous recording of abdominal and bladder pressures).

2.2 Urge incontinence¹

Symptom: The woman experiences involuntary leakage of urine preceded or accompanied by the feeling of urgency. Urge urinary incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency (new ICS definition). Urge

¹The ICS term 'overactive bladder' has not been used in this NfG to avoid confusion. According to ICS overactive bladder denotes the appearance of detrusor contractions during filling cystometry. The ICS also uses the term 'overactive bladder syndrome' which denotes 'urgency with or without incontinence, usually with frequency and nocturia'. In publications and promotion material the two concepts are often mixed up.

incontinence is often associated with an increased frequency of micturition and episodes of urgency not leading to incontinence.

Sign: There is no directly and reliably observable sign of urge incontinence. Pad tests may verify leakage and diaries document episodes of urge incontinence, urgency and micturition frequency and volumes.

Condition: Involuntary detrusor contractions associated with urgency are observed during filling cystometry. This requires the concomitant registration of abdominal and bladder pressure. Urethral pressure should preferably also be monitored, as a drop in urethral pressure, representing a premature micturition reflex may precede a detrusor contraction associated with urgency. The symptoms and signs of urge incontinence often appear in patients with a normal filling cystometrogram. It is not known whether these women in fact have a different condition.

2.3 Mixed incontinence

Symptom: Mixed urinary incontinence is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing (new ICS definition)

Sign: Sign of both stress and urge incontinence (see above) are observed.

Condition: The conditions of stress and urge incontinence (see above) are both present.

3. PHARMACODYNAMICS

Pharmacodynamics for drugs against stress or urge incontinence is mainly studied using urodynamic methods. Urodynamic studies, which are used for diagnosis at a condition level, should be performed early in the development of a new substance in order to demonstrate the effect on the bladder or the urethra of the medicinal product. The types of urodynamic studies to be used differ between stress and urge incontinence. Urodynamic procedures and interpretation of findings should be strictly standardised in the protocol and between participating centres. Three independent readers should preferably read cystometrograms. The consensus of two readers will suffice to verify findings. Urodynamic investigations are often useful in early dose-finding and may also be used in PK/PD studies.

Secondary pharmacodynamics should be studied as appropriate for the drug substance.

3.1 Stress incontinence

Urethral pressures at rest (maximum urethral [closure] pressure, urethral [closure] pressure profile, functional profile length) provide basic data on urethral closure function. Closure function is, however, the result of a complex interplay between the urethra and surrounding tissues during an increase in abdominal pressure (stress/effort). The effect of the medicinal product on urethral closure function during an increase in abdominal pressure can be studied by measuring abdominal leak point pressure (LPP). LPP denotes the abdominal pressure increase needed for incontinence to appear. The pressure increase may be brought about by a series of coughs of increasing intensity (cough induced LPP) or by Valsalva provocation (Valsalva LPP). Abdominal pressure measurement may be obtained vaginally, rectally or in the bladder. It is recommended that the appearance of leakage should be detected by a urethral conductance meter or by using X-ray videography to allow precision in the measurement.

3.2 Urge incontinence

Filling cystometry may give information on effects on bladder sensation during filling, abnormal detrusor activity, bladder capacity and bladder compliance.

3.3 Mixed incontinence

For the indication mixed incontinence, urodynamic studies on both stress and urge incontinent patients should be made to demonstrate an effect of the drug on both the bladder and the urethra.

4. CLINICAL OUTCOME MEASURES

This section lists a number of possible end-points that can be used in phase II and III studies. It is not expected that all endpoints will be used in all studies. The selection to be used may vary with the aim of the study.

The primary aim for developing new drugs for urinary incontinence should be to obtain a subjective improvement or cure of symptoms for the patient. Changes in symptom measures allow a quantification of changes but cannot serve as surrogate end-points for subjective perception of effect.

4.1 Subjective outcome measures

The overall outcome of treatment as perceived by the patient should be recorded by simple scales. Examples are given below:

1. Likert scale, e.g. "My condition (e.g. urinary problems, urinary incontinence) causes me no problems, very minor problems, minor problems, moderate problems, severe problems, very severe problems.
2. Treatment benefit, e.g. "My condition (e.g. urinary problems, urinary incontinence) has been cured, improved, not changed, worsened during treatment".
3. Visual analogue scale with end-points, e.g. "my urinary incontinence/ urinary problems causes me no problems and my urinary incontinence/ urinary problems causes me intolerable problems".

4.2 Quantification of symptoms

4.2.1 Diaries

A diary kept by the patient before and during treatment can include several variables of value for evaluating the effectiveness of treatment. Such variables are

- the time (frequency) of micturitions
- the volume of each micturition
- the occurrence of incontinence
- the occurrence of episodes of urgency without incontinence
- the number of protective pads used
- the amount of urine leaked in each protective pad (see below)

The information gathered allows calculating quantitative data and their change during treatment:

- frequency of micturition (diurnal and nocturnal)
- volume voided per micturition
- total volume voided per time period
- mean voided volume

- largest single void
- incidence of incontinence episodes
- incidence of episodes of urgency
- number of protective pads used per time period
- amount of urine leaked per time period (see below)

A diary including only recording of events (micturition, leakage, urgency and pad use) should and could usually be kept for a complete week. A diary including measuring of volumes and pad weight increase should be kept for as long a period as possible, usually for 48-72 hours but never less than 24 hours.

The symptom of urgency can be defined as “the sudden compelling desire to pass urine, which is difficult to defer”. This is a rather vague definition that is open to different interpretations. Investigators are urged to use more descriptive terms for the degree of urgency felt by the patient at each micturition².

The circumstances under which the diary is kept should be approximate to those of everyday life, and should be similar before and after intervention to allow for meaningful comparison.

4.2.2 Pad weighing tests

By weighing protective pads before and after use, the amount of urine leaked into the pad can be measured. In this way urinary leakage can be quantified.

Pad weighing tests can be divided into short-term tests, generally performed under standardised conditions, and long-term tests, generally performed by the patient at home during 24-48 hours.

Reproducibility of the tests improves if the circumstances are standardised as much as possible (e.g. bladder filling in short term tests and activities in long term tests). For long term tests reproducibility increases with the length of the period measured.

4.2.3 Quality of life

Disease specific and generic instruments for measuring health-related quality of life (HRQL) can be used in trials of products for urinary incontinence. The instruments used should be properly validated in the target population. A clinically relevant change in prespecified 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 Indication of the SPC, but may, if clinically relevant changes have been found, be included in other parts of the SPC (e.g. section 5.1 Pharmacodynamics).

² For example: 1. No urgency, I felt no need to empty my bladder, but did so for other reasons. 2. Mild urgency, I could postpone voiding as long as necessary, without fear of wetting myself. 3. Moderate urgency, I could postpone voiding for a short while, without fear of wetting myself. 4. Severe urgency, I could not postpone voiding, but had to rush to the toilet in order not to wet myself. 5. Urge incontinence, I leaked before arriving to the toilet.

5. STUDY DESIGN AND CHOICE OF END-POINTS

5.1 Therapeutic exploratory and dose response studies (phase II)

5.1.1 Selection of patients

The highest level of diagnosis (condition, see section 2.) is generally recommended in phase II studies but diagnosis at the sign level may be accepted. Stress and urge incontinence should be studied separately.

5.1.2 Choice of end-points

The focus of these studies is usually urodynamic but subjective and objective (e.g. incontinence episodes, urinary frequency, urinary urgency, volumes voided etc). Signs and symptoms should also be reported.

5.1.3 PK/PD studies

Especially for stress incontinent women, episodes of leakage may often be predicted in relation to certain activities. The product may then be used on an "as needed" basis. For such use PK/PD data are useful. LPP measurements can be used to provide such data.

5.1.4 Design

Parallel group design including one placebo arm is recommended (see also 5.2.4). The duration of phase II studies should be long enough to include the time for reaching maximal effect.

5.2 Confirmatory studies (phase III)

5.2.1 Selection of patients

The diagnostic level of the patients included should be defined and stated. Diagnosis at the sign level is acceptable in large phase III multicentre trials³. In urge incontinence this requires that symptomatic effect has previously been shown in patients both with and without detrusor contractions during filling cystometry as these patients may have different etiologies for their symptoms.

It is recommended to primarily include patients with "pure" stress incontinence or urge incontinence to studies of stress or urge incontinence. For practical reasons it is, however, often necessary to include patients with mixed incontinence in both kind of studies. In such cases the protocol should define the degree of stress or urge that is allowed for inclusion in a study of urge or stress incontinence. It is important that the kind of incontinence to be studied is the major complaint of the patient. The inclusion of patients with mixed incontinence into studies of stress or urge incontinence will not allow an indication of mixed incontinence and may complicate interpretation of study results, e.g. the effect on the number of incontinence episodes.

For studies of a drug aimed at treatment of mixed incontinence the protocol should define the degree of each component necessary for inclusion.

If a drug is intended for use in patients with urinary urgency and increased urinary frequency but with no incontinence (the urgency-frequency syndrome without incontinence according to

³ There are two reasons for this: 1. It is very difficult to standardise the urodynamic investigation between centres. 2. In clinical practise urodynamic investigations are seldom made and the trial will then be closer to clinical reality.

ICS), such patients should be studied separately or as a stratified subgroup within a larger study.

5.2.2 Choice of end-points

The choice of primary end-points may vary between studies. Most important is to document the absolute and relative effect on the subjective perception of treatment by the patient (see 4.1). Results should primarily be given as cure rates and responder rates. The clinical relevance of any specific responder definition should be justified in the protocol of the study.

At least one quantitative symptom variable (see 4.2) should always be included in studies as co-primary end-point. The choice of co-primary end-points will depend on the aim of the study and the inclusion criteria. For stress incontinence the incidence of incontinence episodes and/or amount of urine leaked may be used. For urge incontinence the incidence of incontinence episodes, the incidence and intensity of urgency and/or the frequency of micturition are recommended as co-primary end-points. The latter may be chosen in patients with urgency without incontinence. Other quantitative variables may provide supportive evidence and should be used as secondary end-points.

In stress incontinence, the drop out rate for subsequent surgery may serve as an informative end-point.

5.2.3 Comparator

As long as no drug has been approved for stress incontinence, studies should be placebo controlled. Comparisons with non-drug therapies (e.g. pelvic floor exercise, vaginal devices) are encouraged but may pose problems with study design.

As available drugs for urge incontinence do not consistently show superiority to placebo, a placebo arm should be included in trials of drugs against urge incontinence. Alternatively more than one dose of the drug tested can be used if early studies indicate an apparent dose response relationship. A comparator arm including the best available treatment should be used to allow claims of superior efficacy or safety.

5.2.4 Design

In trials of drugs against urge incontinence the placebo effect is often pronounced. This may in part be due to a “learning” effect from too frequent use of diaries during the trial. This “learning” effect should be taken into account in the timing of efficacy assessments. If time to onset of action and time to maximum efficacy has been established in phase II trials, base-line and end of study assessments may be sufficient. Possible carry-over effects limit the usefulness of crossover design. Parallel group design is recommended for studies of urge incontinence.

The experience of studies of drugs against stress incontinence is limited. Early studies may provide a basis for the choice of crossover or parallel group design (e.g. the size of the placebo effect, AEs that may allow unblinding of treatment).

Controlled confirmatory studies of at least 3 months duration are recommended.

Open label extensions of at least one year should be utilised to obtain long term safety information. Randomised placebo-controlled withdrawal periods in such studies may provide information on the need for prolonged treatment and possible loss of efficacy over time and are therefore recommended.

5.3 Specific safety aspects

Drugs intended for use in stress or urge incontinence may affect bladder emptying. It is therefore important to monitor patients for increases in residual urine and urinary tract infections.