Veröffentlichung von Ergebnissen aus abgeschlossenen nicht-interventionellen Studien (NIS) im VFA-Studienregister:

**NIS Grunddaten:**

**Studientitel:**
A Prospective, Observational Study of Men With Premature Ejaculation Who Are Treated With PRILIGY® or Alternate Care

**Zielsetzung / Fragestellung:**
This is an international, non-interventional study, designed to evaluate the use and safety profile of PRILIGY® in the post-approval period. From clinical daily routine, there is no data regarding the safety of PRILIGY® beside the existing safety-data from randomized clinical trials. This study shall provide further information on PRILIGY® and alternate care/non-PRILIGY® treatment(s) in the clinical practice setting.

**Handelsname:**
PRILIGY®

**Studiennummer:**
R0966769PRE4001

**NIS Abschlussdaten:**

**Methodologie:**
This was an approximately 12-week, prospective, postmarketing, observational study with a 4-week post-observational telephone follow-up contact to collect and evaluate safety data for the labeled use of PRILIGY® and alternate care/non-PRILIGY® treatment (defined as any treatment other than the on-label use of PRILIGY® [e.g., oral, topical, or behavioral]), which were prescribed and/or recommended in routine clinical practice for men with a diagnosis of PE in those countries where PRILIGY® had received initial marketing authorization (i.e., Austria, Finland, Germany, Italy, Portugal, Spain, Sweden) through the Decentralized Procedure that was completed in December 2008. The study consisted of 3 periods, including a pre-observational period with a screening/baseline visit on Day 1, an observational period consisting of approximately 3 study visits (defined as Visits 2 to 4) that were anticipated over a period of approximately 12 weeks, although patients were instructed to return for study visits according to local practice, and a post-observational period, which consisted of a telephone follow-up contact approximately 4 weeks after the end of treatment/early withdrawal visit. The intent of the study was to observe and collect data from the participating HCP in the treatment of men with PE in accordance with local practice, although the Summary of Product Characteristics (SPC) for PRILIGY®, including recommendations regarding the intended use of PRILIGY® (e.g., SPC Posology and method of administration, Contraindications, and Special warnings and precautions for use), was provided in the study protocol. All treatment decisions (i.e., PRILIGY® or alternate care/non-PRILIGY®) were made at the discretion of the participating HCP.

**Analysierte Anzahl der Patienten:**
10.028

**Diagnose und Selektionskriterien:**
No specific selection criteria (inclusion or exclusion criteria) were specified to select patients, due to the observational nature of this study. Patients were considered for enrollment in the study only after the participating HCP had determined that either treatment with PRILIGY®, based on the prescribing information in the SPC, or alternate care /non-PRILIGY® treatment was appropriate. Only patients with a current diagnosis of PE, or who were newly diagnosed with PE, and who sought treatment for their condition (i.e., patients who presented spontaneously for evaluation and were not actively recruited by the participating...
HCP) were considered for enrollment in the study. To maintain the observational nature of the study, the participating HCP was instructed not to discuss the possibility of study participation with the patient until after there was an agreement between the participating HCP and the patient as to the appropriate course of treatment.

**Dauer:**

36 month

**Stand der Information:**

PRILIGY®, dapoxetine hydrochloride, is a selective inhibitor of serotonin reuptake that is indicated for the treatment of premature ejaculation. Premature ejaculation prevalence rates vary among studies. Estimates of 20% to 30% are often cited (Laumann 1999; Porst 2007); however, other data suggest that the actual prevalence may be as low as 4% to 5% (Waldinger 2008). The negative consequences of premature ejaculation, such as decreased satisfaction related to sexual intercourse and personal distress, are highly problematic for some men (Hartmann 2005; Symonds 2003). PRILIGY® differs from other drugs in the selective serotonin reuptake inhibitor class as its rapid onset and clearance profile facilitates dosing on an as needed basis. PRILIGY® is indicated for the treatment of premature ejaculation in men 18 to 64 years of age. The following conditions for enrollment were fulfilled in the clinical studies of premature ejaculation:

- An intravaginal ejaculatory latency time of less than 2 minutes; and
- Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes; and
- Marked personal distress or interpersonal difficulty as a consequence of premature ejaculation; and
- Poor control over ejaculation

Based on all of the available data from the clinical development program, PRILIGY® has demonstrated a favorable overall benefit-risk profile in treating patients with premature ejaculation. This study will use an observational approach to provide additional information on the safety profile and use pattern of PRILIGY® and other treatments in clinical practice.

**References:**


**Kriterien der Bewertung – analog ICH E3:**

**Wirksamkeit unter Alltagsbedingungen:**

Efficacy was not assessed in this study.

**Sicherheit:**

Orthostatic vital signs (blood pressure and heart rate [pulse]) were measured during the pre-observational period for patients who were candidates for treatment with PRILIGY®. The following approach was recommended as an acceptable method for measuring orthostatic vital signs:
• The first measurement should be taken with the patient in the supine position for at least 2 minutes, and recorded.
• The second measurement should be taken with the patient in the standing position (or sitting position if unable to stand) for at least 2 minutes after the supine measurements but before 3 minutes, and recorded.

Adverse Events

Safety and tolerability were evaluated throughout the study by incidence, severity, and type of adverse events, serious adverse events, adverse events of special interest, and physical examination results (at screening/baseline, and at any other time during the study that the participating HCP deemed it medically necessary). Safety was reviewed on a regular basis by an internal safety working group to detect potential safety signals associated with the use of PRILIGY® in the post-approval setting.

Syncope was identified as an adverse event of special interest in this study. In addition to syncope, other adverse events that were reported on the Adverse Event Case Report Form (CRF) were classified in the Statistical Analysis Plan (SAP) as adverse events of special interest according to the identified and potential risks identified in the Risk Management Plan (RMP) for PRILIGY® (Mood and Related, Neurocognitive Related, Cardiovascular System, Urogenital System and Sexual Function, Accidental Injury, Abnormal Bleeding, and Others). Such events were identified through a search of all adverse event terms in the clinical database using the same search strings that were developed for previous clinical study reports and the Summary of Clinical Safety. An independent Syncope Adjudication Committee (SAC) was established to adjudicate possible events of syncope as to whether or not loss of consciousness had actually occurred.

Statistische Methoden – analog ICH E3:

Methoden:
Statistical analyses were exploratory and descriptive in nature. All statistical considerations, including derived variables, proposed format, and content of tables was detailed in the SAP. The All Enrolled Patients Analysis Set was defined as all patients for whom information was entered into the database. All patients who took at least one dose of PRILIGY® were included in the Safety Analysis Set associated with PRILIGY® treatment, while all patients who did not use PRILIGY® at Visit 1 and used alternate care/non-PRILIGY® treatment at Visit 1 were included in the analysis associated with alternate care/non-PRILIGY® treatment.

A patient was considered to have completed the study if he had completed the end-of-observation assessments during the observational period. Patients who prematurely discontinued study treatment (PRILIGY® or alternate care/non-PRILIGY®) for any reason before completion of the observational period (approximately 3 study visits [defined as Visits 2 to 4] were anticipated over a period of approximately 12 weeks) were not considered to have completed the study.

While patterns of use and safety data were collected for both treatments, the patient characteristics between the groups were expected to be different because of 1) possible selection bias in the determination of treatment (e.g., orthostatic testing, comorbidities, and prior treatment history might have formed the basis for the treatment decision), 2) the diversity of treatments prescribed in the alternate care/non-PRILIGY® group, and 3) contraindications associated with PRILIGY® and the different alternate care/non-PRILIGY® treatment options. All of these factors increase the likelihood of bias, while the same patient population characteristics/demographics were not necessarily expected to be similar among both groups (PRILIGY® and alternate care/non-PRILIGY®). Therefore, such circumstances would challenge the interpretation of the results of any direct statistical comparison. Several subpopulations of patients sharing common characteristics (e.g., patient age, medical history of cardiovascular or psychiatric conditions) however were identified, such that safety data observed in the alternate care/non-PRILIGY® group could provide perspective among the incidence of adverse events among patients who were treated with PRILIGY®.

No formal interim analyses were planned for this study, however interim safety data reviews were conducted periodically as noted in the SAP, while one interim safety report was issued and submitted to health
authorities in response to regulatory review during the course of the study.

Zusammenfassung – analog ICH E3:

Ergebnisse zur Wirksamkeit unter Alltagsbedingungen:

Efficacy was not assessed in this study.

Ergebnisse zur Sicherheit:

Overall, TEAEs were reported by 12.0% and 8.9% of patients who were treated with PRILIGY® and alternate care/non-PRILIGY®, respectively. The incidence of TEAEs was greatest for patients who were treated with alternate care (oral drug) (16.1%), and lowest for patients who were treated with alternate care (non-oral) treatment (3.5%). Adverse events were most commonly reported in the gastrointestinal disorders and nervous systems disorders system organ classes (SOCs). Overall, the most commonly reported TEAEs (≥1% in any group) were nausea (2.4%), headache (1.9%), and vertigo (0.8%), with a higher incidence in patients who were treated with PRILIGY® (3.1%, 2.6%, and 1.0%, respectively) than in patients who were treated with alternate care (oral drug) (2.3%, 1.3%, and 0.9%, respectively) or alternate care (non-oral) (0.1%, 0.3%, and 0%, respectively). The majority of TEAEs reported in either group was mild or moderate in severity, resulted in no change in treatment, and was resolved by the time that the patient completed or withdrew from the study.

The overall incidence of TEAEs was greater in patients who increased their dose of PRILIGY® from 30 to 60 mg (15.0%) than those who remained on the 30-mg dose for the duration of the study (10.9%). The incidence of TEAEs was reported more frequently (12.9%) for those who were titrated to PRILIGY® 60 mg at Visit 2 than for those who remained on PRILIGY® 30 mg for the duration of the study (4.8%), although for those who remained on PRILIGY® 60 mg at Visits 3 and 4, the incidence of TEAEs was less at Visit 2 (10.5% and 8.7%, respectively). Treatment-emergent adverse events were most frequently reported in the gastrointestinal disorders and nervous system disorders SOCs, with a greater incidence in patients who increased the dose of PRILIGY® from 30 to 60 mg (5.4% and 5.2%, respectively) than those who remained on the 30-mg dose of PRILIGY® for the duration of the study (4.2% and 3.6%, respectively).

At Visit 2, the incidence of adverse events was similar, but less severe, for patients who had their dose of PRILIGY® increased from 30 to 60 mg compared with those who remained on the 30-mg dose for the duration of the study (6.3% versus 7.0%, respectively). In addition, patients who were titrated to PRILIGY® 60 mg at Visit 2 had a lower incidence of possibly prodromal adverse events than those who remained on the 30-mg dose for the duration of the study (2.0% versus 2.4%), while patients who were down titrated from 60 to 30 mg of PRILIGY® reported a greater incidence of TEAEs than those who remained on either 30 or 60 mg of PRILIGY® for the duration of the study.

The overall incidence of TEAEs was greater in patients who were ≥65 years of age (21.4%, PRILIGY®; 7.5%, alternate care/non-PRILIGY®) than in patients who were <65 years of age (11.9%, PRILIGY®; 8.9%, alternate care/non-PRILIGY®), although the sample sizes were small. Among the patients who were treated with PRILIGY®, vertigo and fatigue were reported at a greater incidence in patients who were ≥65 years of age (3.1% and 2.0%, respectively) than in those patients who were <65 years of age (1.0% and 0.3%, respectively). No TEAEs were reported in patients who were ≥65 years of age and received alternate care (non-oral) treatment.

There were no reports of death among patients who were treated with either PRILIGY® or those who were treated with alternate care/non-PRILIGY® in the study. A total of 22 patients in the Safety Analysis Set reported treatment-emergent serious adverse events during the study, 12 (0.2%) patients treated with PRILIGY® and 10 (0.3%) patients treated with alternate care/non-PRILIGY®. All of the serious adverse events were considered not related to treatment with PRILIGY® or alternate care/non-PRILIGY® by the participating HCPs.

The incidence of patients that discontinued from the study due to a TEAE was greater in patients who were treated with PRILIGY® (1.5%) than in patients who were treated with alternate care/non-PRILIGY® (0.2%), although no TEAE led to the discontinuation of more than 0.3% of patients in either treatment group. Of the TEAEs of special interest, nausea, hypotension, dizziness postural, orthostatic hypotension, and presyncope resulted in discontinuation in patients who were treated with PRILIGY® only, although the incidence of discontinuations resulting from each of these TEAEs was low (0.3%, <0.1%, <0.1%, <0.1%, and <0.1%, respectively).
respectively).

Overall, the total incidence of TEAEs of special interest in each of the adverse event categories was low. Treatment-emergent adverse events of special interest were most commonly reported in the neurocognitive-related adverse event category (2.0%). With the exception of the cardiovascular system (PRILIGY®, 1.6%; alternate care [oral drug], 1.3%) and accidental injury (0.1%; for both), TEAEs of special interest in each adverse event category was greater for patients who were treated with alternate care (oral drug) than PRILIGY®.

There were no associations between TEAEs of syncope and orthostatic test results. One event of syncope was reported as a serious adverse event in a patient who was treated with alternate care/non-PRILGY (paroxetine), which was adjudicated as syncope with loss of consciousness by the SAC. It was reported by a patient in Finland who presented to the hospital with severe syncope, photophobia, and muscular weakness that he experienced 5 or more days after taking his last dose of paroxetine. The participating HCP did not consider any of the events to be related to his treatment with paroxetine, the events resolved, no action was taken with paroxetine, and the patient completed the study.

Ergebnisse zu anderen Parametern:

Not applicable

Schlussfolgerung:

Overall, the types of adverse events observed in this postmarketing observational study is consistent with the safety profile presented in the SPC for PRILIGY®, although the incidence rates of these events are less than those observed during clinical development. Participating HCPs generally followed the prescribing instructions in the SPC by initiating patients on the 30-mg dose of PRILIGY® and by selecting patients according to the recommendations in the SPC (e.g., Posology and method of administration, assessing orthostatic tolerance before the initiation of PRILIGY®, avoiding the use of PRILIGY® in patients who have medical histories or use concomitant medications listed in the Contraindications and Special warnings and precautions for use). However, some patients with cardiovascular or psychiatric conditions contraindicated by the SPC were treated with PRILIGY®. The Patient Brochure and PIL were found to be adequate by the large majority of participating HCPs and patients. The low incidence of adverse events and lack of any events of syncope in PRILIGY®-treated patients in this large, diverse population of men with PE supports tolerability of PRILIGY® when prescribed in routine clinical practice, suggesting that the current risk minimization measures for its identified and potential risks, including syncope, are effective.