SYNOPSIS

Name of Sponsor/company: Krewel Meuselbach GmbH	Name of Finished Product: Hedelix® drops	Name of Active Ingredient(s): Ivy leaves extract

Confidentiality statement:
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Title of the study:
Hedelix® Ability: Acute bronchitis therapy with ivy leaves extracts in a two-arm study. A double-blind, randomised study vs. active comparator

EudraCT number: 2007-003272-19

Investigators:
Multicentre; no principal investigator was defined

Study centre(s):
Multicentre, Czech Republic

Publication:
Cwientzek U., B. Ottillinger, P. Arenberger: Acute bronchitis therapy with ivy leaves extracts in a two-arm study. A double-blind, randomised study vs. an other ivy leaves extract. Phytomedicine 18: 1105-1109 (2011)

Study period:	**Clinical Phase**: IIIb
09 Apr 2008 (first enrolment) 23 Apr 2009 (last completed)	

Objectives:
To compare an ivy leaves extract (Hedelix®) to an active control (Prospan®, another ivy leaves extract) with the aim to establish the efficacy and tolerability in patients with acute bronchitis.

Methodology:
Double-blind, randomised, controlled parallel group comparison vs. an active control

Number of patients:
Planned: 590 total, 295 per treatment group.
Recruited: 590 total (Hedelix®: n=295; Prospan®: n=295) – Safety population
Analysed: 588 total (Hedelix®: n=293; Prospan®: n=295) – Intention-to-treat population
518 total (Hedelix®: n=260; Prospan®: n=258) – Per-protocol population

Diagnosis and main criteria for inclusion:
Inclusion: Male or female patients at least two years of age with a confirmed clinical diagnosis of acute bronchitis with a Bronchitis Severity Score (BSS) ≥ 5 (of 20) and a duration of complaints not more than 48 hours.
Exclusion: Patients with prior or intended concomitant medication influencing the course of acute bronchitis and/or the target criteria of the study, especially therapy with antibiotics, beta-2 agonists, and/or antihistamines; patients with chronic bronchitis or with allergic asthma or bronchial hyperreactivity.

Test product, dose and mode of administration, batch number:
Hedelix® s.a. (Ethanolic extract (50%) of ivy leaves)
Single dose: Adults and children >10 years old: 24 drops
Children between >4 and ≤10 years old: 16 drops
Children between ≥2 and ≤4 years old: 12 drops
Daily dose: Three single doses
Batch number: Supplied with the certificate of analysis in Appendix 16.1.8 of the study report

Duration of treatment:
Seven days (±1 day)

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Reference therapy, dose and mode of administration, batch number:
Prospan® Hustentropfen (Ethanolic extract (30%) of ivy leaves)
Single dose: Adults and children >10 years old: 24 drops
Children between >4 and ≤10 years old: 16 drops
Children between ≥2 and ≤4 years old: 12 drops
Daily dose: Three single doses
Batch number: Supplied with the certificate of analysis in Appendix 16.1.8

Criteria for evaluation:
Efficacy:
Primary: Bronchitis Severity Score (BSS)
Secondary: BSS component symptoms
Further clinical symptoms (body temperature, hoarseness, headache, pain in limbs or back, fatigue/exhaustion)
Investigator's global efficacy evaluation
Patient's global evaluation of satisfaction with therapy
Ability to go to work or school

Safety:
Investigator's global tolerability evaluation
Patient's global tolerability evaluation
Adverse Events

Statistical methods:
Primary endpoint: The aim of this clinical trial was to establish the efficacy of the ivy leaves extract (Hedelix®). For this purpose, the mean improvement of BSS at Visit 3 (Day 7±1) vs. baseline was compared between the treatment groups. Efficacy was assumed if the mean improvement of BSS vs. baseline observed in the group receiving the ivy leaves extract (Hedelix®) was non-inferior to that observed in the active control group (Prospan®). The border of non-inferiority was 32% of the standard deviation of BSS change observed in the active control group, because the expected superiority over placebo would be approximately 64% of the standard deviation. Efficacy could also be assumed if the two-sided 95% confidence interval of treatment difference of the ivy leaves extract vs. the active control was completely above the lower limit, i.e. - 64% of the standard deviation of BSS change observed in the active control group.
Hypotheses were tested using an analysis of covariance with the two factors treatment group and site, and with the baseline value as a covariate. The factor of site was taken as a random. Significance was assumed if $p<0.05$ (two-sided). Two-sided 95% confidence intervals (CI) of treatment difference were calculated within the frame of ANCOVA. It means that CI was adjusted for baseline inhomogeneities. Statistical tests were performed for the PP population and, secondarily, for the ITT population. As the ivy leaves extract (Hedelix®) proved to be non-inferior to the active control group (Prospan®), its superiority vs. the active control group was tested. This test was performed for the ITT population and, secondarily, for the PP population. This procedure keeps the overall significance level of 5%.

Secondary endpoints: BSS subscales, clinical symptoms incl. body temperature as well as global evaluations of efficacy, tolerability, or satisfaction with therapy were compared between groups by t-tests, Mann-Whitney tests or Fishers exact test, as adequate for the scale. The ability to go to work or school, university, kindergarten, or day nursery was described using survival curves with the event "able to go to work or school, university, kindergarten, or day nursery". Log rank test were used for comparison of groups. Furthermore, responders were calculated from changes in BSS according to three predefined definitions. Responder rates were compared between groups using Fishers exact test. All p-values for secondary endpoints do not possess confirmatory value.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Both from a descriptive and from a formal point of view Hedelix proved to be non-inferior to the reference drug Prospan in improving symptoms of acute bronchitis. The difference between Hedelix and Prospan in improving the Bronchitis Severity Score (BSS) from baseline to Visit 3, the primary endpoint, was fully within the predefined non-inferiority margin. Post-hoc calculations showed that the non-inferiority margin was even narrower than originally planned. This underlines the comparability of both drugs. In addition, also the BSS subscales, additional clinical parameters typical for the disease, and the investigators' and patients' global efficacy evaluations showed that both treatments improved symptoms to a comparable extent, frequently with a small numerical advantage for Hedelix.

Treatment results were almost identical for the ITT and for the PP dataset. This indicates that the study results are not only valid for an artificially monitored study population, but can be expected to apply also to a patient population in everyday practice.

SAFETY RESULTS:

The safety information in this study is based on 590 patients and on a total exposure of 11 patient years in both groups combined. In all safety parameters evaluated, Hedelix and Prospan showed a comparable profile. The mean global tolerability evaluations by investigators and patients gave "good" or better ratings in both groups.

Overall, 2.7% of patients (per group and overall) experienced an adverse event, all of which were non-serious. Fewer patients younger than ten years had adverse events than would have been expected from their share of the study population, indicating a very favourable tolerability especially in children as a major target population.

The majority of patients suffering from an adverse event (≥75% in each group) had gastrointestinal side effects, mostly of the upper gastrointestinal tract. Such reactions are already known and included in the labelling of both study drugs. Intercurrent diseases classified as adverse events occurred in single patients only; in these cases there was no reasonable connection between event and study medication.

Overall, the adverse event and general tolerability profile observed confirmed the favourable tolerability of Hedelix and of Prospan and did not reveal unexpected safety signals for both.

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CONCLUSION:

Hedelix was non-inferior to the reference drug Prospan within a very narrow equivalence corridor in improving symptoms of acute bronchitis. Secondary endpoints like other clinical symptoms of acute bronchitis or the global evaluation of efficacy and satisfaction with therapy confirmed the findings of the BSS and showed that both treatments improved symptoms to a comparable extent, frequently with a small numerical advantage for Hedelix. Results for the intention-to-treat and the per-protocol dataset agreed for all parameters, proving the internal validity of the data. In addition, Hedelix and Prospan had a favourable and comparable safety profile, which confirmed the available safety information. Furthermore, data show that the drugs were very well tolerated especially by children less than 10 years of age.

Prospan was chosen as a reference drug based on its efficacy in previous studies vs. active controls and placebo. Mansfeld et al. found an improvement of pulmonary function tests compared to placebo in children with bronchial asthma (Mansfeld et al. 1998). Pulmonary function tests in children who were hospitalized due to chronic obstructive pulmonary disease showed a tendency towards superiority of the ivy leaves extract over acetylcysteine, a chemically defined standard drug in this indication (Gulyas 2005). In grown-up patients with chronic bronchitis, the ivy leaves extract was compared to ambroxol, another standard drug used for the study indication (Meyer-Wegener et al. 1993). Both drugs showed an improvement of clinical parameters and of pulmonary function tests, again with a tendency towards superiority of the herbal drug. Accordingly it is sufficiently proven that the reference drug is effective and improves pulmonary function and clinical parameters in patients with bronchial diseases.

For a non-inferiority study it is important to apply measurement tools able to differentiate between drugs of different activity, because an insufficiently sensitive parameter might not find efficacy differences between Hedelix and Prospan, if such differences existed. The BSS as the primary efficacy parameter has been used in previous studies in acute bronchitis and was found to be highly sensitive to differentiate between an active drug and placebo. Thus it was a suitable instrument here. In addition, several studies in acute bronchitis found that the BSS decreased by approximately 70–80% vs. baseline in the active groups (Matthys et al. 2003; Kemmerich et al. 2006; Grünwald et al. 2006). This corresponds to our study, where the BSS decreased by 75–78% over the treatment period, which proves the external validity of our data.

As a conclusion, Hedelix has established its efficacy in patients with acute bronchitis by proving non-inferior to a recognized active control within a very narrow equivalence band. The internal and external validity of the study data make it possible to generalize the results to a broader population. The study furthermore confirms the favourable tolerability of Hedelix in an overall and especially in a paediatric population with acute bronchitis.