1 ABSTRACT

Title

A multicentre, European, observational, Drug Utilisation Study (DUS) of BLI800 (Eziclen®/Izinova®) as a bowel cleansing preparation.

Keywords

Non-interventional, international, safety, bowel preparation, oral trisulfate solution.

Rationale and background

Colonoscopy plays an important role in the diagnosis and management of colorectal diseases. This procedure remains the gold standard for the early detection of colorectal cancer. Bowel cleansing is a critical issue in the quality and diagnostic efficacy of this examination as well as for the potential therapeutic procedures.

In January 2013, the European registration procedure was successfully concluded for BLI800 (Eziclen®/Izinova®), an oral solution composed of the sulphate salts of sodium, potassium and magnesium. The postmarketing commitments that accompanied the approvability of this bowel oral preparation requested that Ipsen Pharma SAS conducts a DUS to assess drug utilisation in the real life setting in a representative sample of the European target population.

Research question and objectives

- Primary objective: to document the misuse of BLI800 (Eziclen®/Izinova®), defined as non-compliance in terms of insufficient liquid intake, during the postapproval period in the real life setting.
- Secondary objective: to describe the safety profile of BLI800 (Eziclen®/Izinova®) in routine clinical practice, overall and in case of misuse defined as non-compliance in terms of insufficient liquid intake, and identify any immediate/acute adverse events associated with the use of BLI800 (Eziclen®/Izinova®) in special populations (i.e., the elderly and patients at risk for electrolyte shifts).

Study design

This was a non-interventional, multicentre, European, observational DUS in male and female subjects who have received BLI800 (Eziclen®/Izinova®) in the postmarketing setting.

The study was conducted in four countries where the product is already on the market (the Czech Republic, Poland, Germany and the Netherlands).

Setting

Study sites included specialised gastroenterology and hepatogastroenterology departments (referral centres) and endoscopy departments (non-referral centres), and subjects could be inpatients or outpatients. Subjects eligible for participation in the study required bowel cleansing prior to colonoscopy and were prescribed BLI800 (Eziclen®/Izinova®) in accordance with the terms of the marketing authorisation. To avoid bias in the recruitment of subjects, Investigators were asked to include all consecutive patients consulting for a colonoscopy to

achieve the recruitment target of 76 patients per site during a restricted and defined period. If consecutive inclusions were not feasible (e.g. administrative constraints), and in order not to disturb the medical activities in the Investigator's unit, Investigators were authorised to space the inclusions (e.g. inclusion of one subject after every two, or three subjects), and followed the same recruitment frequency until achievement of the recruitment target. As only sixteen sites were initiated instead of twenty initially planned, upon completion of the initial target of recruitment (76 subjects), the sites were invited to include additional subjects up to the limit of 115 subjects maximum. Overall, 10 sites did include additional subjects (7 sites in Germany, 1 in the Czech Republic, 1 in the Netherlands and 1 in Poland). The modalities for recruitment were to be determined prior to recruitment start.

Subjects were followed longitudinally from prescription of BLI800 (Eziclen®/Izinova®) to after the end of the colonoscopy procedure. Eligible subjects were included at the first visit (prescription). After signing an Informed Consent Form (ICF), details of subject demographics and characteristics, medical and surgical history, indication for bowel preparation, and prior (1 month) and concomitant medications were collected. Vital signs (blood pressure, heart rate, height and body weight) and physical examination findings were to be recorded when available. Electrocardiogram (ECG), and local laboratory test results dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake were recorded when available, at first (prescription) and/or second (colonoscopy) visit. Any concomitant medications taken since the first visit, adverse events (AEs), and patterns and conditions of use of BLI800 (Eziclen®/Izinova®) documentation were collected from the subject at the second visit (colonoscopy). In addition, physical examination findings were recorded and the investigator-assessed cleansing level of the colon at colonoscopy. No additional diagnostic or monitoring procedures were performed, and descriptive methods were used for the analysis of collected data.

For each subject, the study duration was from signing the ICF to discharge after the end of the procedure. The overall study duration was approximately 2 years after first subject in.

Subjects and study size, including dropouts

It was planned to include 1285 patients receiving BLI800 (Eziclen®/Izinova®) with the following inclusion/exclusion criteria:

- Eligibility/inclusion criteria: patients who are eligible for colon preparation with BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation and provide written informed consent.
- Exclusion criteria: patients who are not eligible for colon preparation with BLI800 (Eziclen®/Izinova®) in accordance with the marketing authorisation because of a contraindication for use, or are prescribed another bowel cleansing preparation, or who have not signed the ICF.

This estimation was based on the primary endpoint to allow estimation of the overall proportion of non-compliant subjects (assumed as 50%) with a 2-sided confidence level of 95% and a precision of +/-5%.

Variables and data sources

- Subject demographics and characteristics (age and gender).
- Vital signs (blood pressure, heart rate, height and body weight).
- Physical examination.
- Medical and surgical history.

- Indication for bowel preparation.
- Patterns and conditions of use of BLI800 (Eziclen®/Izinova®)
  - Modalities of prescription (dosing regimen (one day or split dose regimen), diet and hydration instructions)
  - Date(s) and times(s) of intake
  - Patient compliance with the prescription, derived from the recorded remaining volume of BLI800 (Eziclen®/Izinova®) solution, and the time(s), remaining volume and nature of additional clear liquids to maintain hydration.
- Prior (1 month) and concomitant medications.
- Specific test results: ECG and local laboratory results from assessments performed before the anaesthesia and the colonoscopy and dated no more than 7 days before BLI800 (Eziclen®/Izinova®) intake were collected when available. Collection of local laboratory results was restricted to the following list: serum electrolytes, albumin, international normalised ratio (INR), creatinine, liver enzymes, bilirubin, uric acid and glucose.
- Efficacy evaluation
  - Cleansing level of the colon, assessed by the investigator at colonoscopy according to a four level scale.
- Safety evaluation
  - AEs were collected from when the ICF was signed until discharge after the end of the colonoscopy procedure. A patient's leaflet was distributed to the subject at the first visit, on which the subject was instructed to record any AE experienced after product intake and prior to the procedure. The investigator (or authorised delegate) collected the leaflet at the second visit and recorded any AEs in the electronic Case Report Form (eCRF). During the second study visit, AEs were collected by the investigator from the patient's leaflet, and the patient's interview and medical exam. The investigator decided on the requirement for any follow up of AEs persisting beyond discharge after the procedure according to normal clinical practice.
  - The overall incidence of AEs was presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT), and by number and percentage

<u>Primary endpoint:</u>

The primary objective being the description of non-compliance in terms of insufficient liquid intake, a descriptive analysis of the volume of water and clear liquids taken to maintain hydration was performed and constituted the primary variable. The volume of water and clear liquids taken were derived from the remaining volumes as recorded on the patient's leaflet and reported by the Investigator on the eCRF.

Compliance with the hydration guidelines (2 L of water or clear liquids) is expressed in terms of a ratio (actual volume taken versus theoretical volume) and is classed as follows:

- Excellent: 1:1 if compliance = 100%,
- Good: ≥3:4 and <1:1 if compliance ≥75% and compliance <100%,
- Low: <3:4 and ≥1:2 if compliance ≥50% and compliance <75%,
- Bad: <1:2 if compliance <50%

The primary endpoint was the proportion of non-compliant subjects defined as having taken less than 75% of the prescribed hydration volume (2 L).

This proportion and its corresponding 95% confidence interval (CI) are presented for the overall population as well as for each of the special populations, gender, countries, and each of the dosing regimens.

Data Sources:

The data were collected and recorded on:

- The patient's leaflet (modalities of prescription including dosing regimen, date(s), time(s) and remaining volume of BLI800 (Eziclen®/Izinova®), time(s), remaining volume and nature of clear liquids, and AEs).
- An eCRF. The data collected on the patient's leaflet were recorded in the eCRF by the Investigator (or authorised delegate).

All the collected data were to be in accordance with the daily practice of health care providers.

Start of data collection: The date from which information of the first study subject was first recorded in the study dataset.

End of data collection: The date from which the analytical dataset was completely available.

Results

Subjects Disposition

Following the first monitoring visit at Centre PPD (Poland), major deviations on data quality were evidenced at the site and enrolment was stopped; 13 subjects were included by then. Despite numerous attempts, it was not possible to resolve the open queries on some data collected at this site. Following study data review, it was therefore decided to exclude all included subjects (N=13) from the registry and complete populations. To verify that exclusion of the data had no impact on final study results, subjects demographics were described including and excluding site PPD . CCI [redacted] These subjects are also included in the safety population.

Of the 1281 subjects included, 1231 subjects (96.1%) completed the study (subjects treated, attending the second visit whether or not the colonoscopy was performed). Among the 47 subjects who withdrew, 14 subjects (29.8%) were lost to follow-up, 9 subjects (19.1%) withdrew consent, 6 subjects (12.8%) withdrew due to an AE, and 18 subjects (38.3%) withdrew for other reasons (colonoscopy cancelled by the subject or colonoscopy not necessary anymore).

The total number of subjects from special populations as defined in the protocol (elderly subjects and subjects at risk for electrolyte shifts) (N=544) is above the planned sample size (N=385). However, the majority of special populations is constituted by elderly subjects. The proportion of elderly subjects (502/1281) is in accordance with what was observed in registration studies for BLI800 (Eziclen®/Izinova®) (30% of total population). Regarding recruitment of subject populations at risk for electrolyte shifts, specifically subjects with renal or liver disease or subjects with hyperuricaemia, in this real life study, complete medical history was not always available to the Investigator. Similarly, laboratory tests are not mandated prior to performing a colonoscopy, and as a consequence were rarely done (laboratory data available in 44.7% of the subjects). Thus, the number of subjects with hepatic (N=31) or renal (N=11)

disease, hyperuricaemia (N=52) may have been higher than the number identified through medical review. Subjects with inflammatory bowel disease (IBD) were included in the safety review under the "special populations" heading because BLI800 (Eziclen®/Izinova®) is contraindicated in active IBD. A total of 43 subjects with IBD were enrolled.

Demographic and baseline characteristics

Amongst the 1281 included subjects, the overall mean (± standard deviation (SD)) age was 59.2 (±13.5) years, the median age was 61.0 years, with 779 subjects (60.8%) aged <65 years, and 502 subjects (39.2%) aged ≥65 years.

Overall, there was an equal number of male subjects (647 (50.5%)) and of female subjects (634 (49.5%)) included in the study. However, there were slightly more male than female subjects in the elderly subpopulation (54.2% versus 45.8%).

The overall mean (±SD) height was 170.9 (±9.7) cm, the mean weight was 78.5 (±16.4) kg, and the mean body mass index (BMI) was 26.74 (±4.84) kg/m^2. Height and weight were not reported in a third of the subjects and these results may not be considered as representative of the whole population.

Exclusion of the 13 subjects (M: 4; F: 9) from centre PPD did not impact demographic characteristics. At this centre, 3 of the subjects were > 65 years and none belonged to one of the special populations.

German centres enrolled over half of the subjects and the preponderance of younger (<65 years) versus older (≥65 years) subjects was apparent. Conversely, in the Netherlands, the majority of subjects were elderly. This was due to the fact that screening colonoscopies were directed toward older individuals at the time of study enrolment in this country.

Compliance

Overall, compliance to the hydration guidelines was high. Most subjects from the registry population had a compliance assessed as excellent (1022 subjects (86.8%)) or good (90 subjects (7.6%)) for a total of 94.5% (95% CI (93.0; 95.7)) of subjects with compliance ≥ 75%. A total of 65 subjects (5.5%, 95% CI (4.3; 7.0)) were considered as non-compliant with the hydration guideline (39 (3.3%) had a low compliance and 26 (2.2%) had a bad compliance).

Compliance in special populations

Most subjects ≥65 years from the registry population had a compliance assessed as excellent (386 subjects (84.5%)) or good (37 subjects (8.1%)) for a total of 92.6% (95% CI (89.8; 94.8)). A total of 34 subjects were considered as non-compliant with the hydration guideline (21 (4.6%) had a low compliance and 13 (2.8%) had a bad compliance) for a total of 7.4% (95% CI (5.2; 10.2)).

No formal statistical comparison was made between compliance in subjects <65 and ≥65 years. However, the 95% CIs overlap and a significant difference is unlikely. A total of 95.7% of the subjects <65 years (95% CI (93.9; 97.1)) and 92.6% of the subjects ≥65 years (95% CI (89.8; 94.8)) were compliant to the hydration guidelines.

The same observation was made according to the gender. A total of 95.0% of the male subjects (95% CI (93.0; 96.6)) and 93.9% of the female subjects (95% CI (91.6; 95.7)) were compliant to the hydration guidelines.

The compliance to the hydration guideline of subjects in special populations (elderly subjects, subjects with suspicion of liver disease/hepatic insufficiency, subjects with renal insufficiency, with hyperuricaemia or history of gout, and subjects with IBD) was similar to those who were

not included in special populations. However, as the number of subjects in these populations are small, interpretation must be cautious.

Compliance to treatment intake and preparation intake/solution intake ratio

Overall, on average 96.8% (±13.5%) of the volume of the treatment was taken by the subject. A total of 46 subjects (3.9%, 95% CI (2.9; 5.2)) were considered as non-compliant with the BLI800 (Eziclen®/Izinova®) solution intake (volume taken <75%)

Overall, 1094 subjects (92.9%, 95% CI (91.3; 94.3)) from the registry population had an adequate ratio (compliance >75% for both the BLI800 (Eziclen®/Izinova®) solution intake and hydration) for both first dose and second dose.

Cleansing level

The cleansing level of the colon was assessed by the Investigator at the colonoscopy and, overall, more than 87.6% of the complete population had a cleansing level good (44.0%, 95% CI (41.1; 46.8)) or excellent (43.6%, 95% CI (40.8; 46.5)), which is in agreement with the level of compliance with the hydration guideline and with the BLI800 (Eziclen®/Izinova®) solution intake.

Safety

A total of 374 subjects (31.0%) reported at least one treatment emergent adverse event (TEAE). The majority of TEAEs were considered mild or moderate in intensity and related to the treatment. Of these, 329 subjects (27.3%) experienced 758 TEAEs considered related to the treatment.

No difference was observed in the number of TEAEs between subjects who were non-compliant and subjects who were compliant to the hydration guidelines. A total of 26/86 non-compliant subjects (30.2%, 95% CI (28.0; 41.1)) and 348/1120 compliant subjects (31.1%, 95% CI (28.4; 33.9)) reported at least one TEAE.

A total of 242 subjects from <65 years (32.8%, 95% CI (29.4; 36.3)) and 132 subjects from ≥65 years (28.2%, 95% CI (24.2; 32.5)) reported at least one TEAE. The majority of TEAEs (497/568 and 261/317, respectively for subjects <65 years and ≥65 years) were considered as related to the treatment. Two serious TEAEs, both unrelated to the treatment, were observed in two subjects ≥65 years.

A total of 128 male subjects (20.7%, 95% CI (17.6; 24.1)) and 246 female subjects (41.8%, 95% CI (37.8; 45.9)) reported at least one TEAE. Most of these were considered related (110/128 male subjects, 219/246 female subjects). The frequency of TEAEs was therefore doubled in female subjects. Nausea was the most frequent and was reported in 21.6% (95% CI (18.5; 25.1)) of female and 7.4 (95% CI (5.5; 9.8)) of male subjects. The nature of AEs was overall similar. There was no difference in intensity between genders and the majority of TEAEs was considered mild or moderate in intensity and related to the treatment.

Out of the 28 subjects with suspicion of liver disease/hepatic insufficiency, 7 subjects (25.0%) reported a total of 15 TEAEs including 10 in 5 subjects (17.9%) which were considered as related to the study product.

Out of the 10 subjects with renal insufficiency, 2 subjects (20.0%) reported a total of 7 TEAEs of which all but 1 were considered as related to the study product.

Out of the 49 subjects with hyperuricaemia or history of gout, 15 subjects (30.6%) reported a total of 33 TEAEs including 27 in 12 subjects (24.5%) which were considered as related to the study product. No event of gouty attack was reported.

Out of the 41 subjects with IBD, 13 subjects (31.7%) reported a total of 27 TEAEs including 23 in 11 subjects (26.8%) which were considered as related to the study product.

The majority of related TEAEs were observed in the SOC "Gastrointestinal Disorders" (273 (22.6%) subjects), in the SOC "Nervous system disorders" (87 (7.2%) subjects), and in the SOC "General disorders and administration site conditions" (51 (4.2%) subjects) and in the SOC "Ear and labyrinth disorders" (16 (1.3%) subjects).

No acute/immediate adverse event was identified following intake of BLI800 (Eziclen®/Izinova®) in these special populations.

One death occurred during the study; an PPD who had severe PPD and severe PPD diagnosed before the BLI800 (Eziclen®/Izinova®) administration. The Investigator assessed the event as being not related to the study drug.

A total of 4 serious AEs (SAEs) occurred during the study, all considered as not related to the study product.

Conclusion

In conclusion, the study filled the primary objective to document the misuse of BLI800 (Eziclen®/Izinova®), defined as non-compliance in terms of insufficient liquid intake, during the postapproval period in the real life setting. This misuse was infrequent, with 94.5% of subjects having 75% and above compliance. Non compliance was not associated with a clinical signal for dehydration related averse events.

The safety profile of BLI800 (Eziclen®/Izinova®) in routine clinical practice, overall and in case of misuse defined as non-compliance in terms of insufficient liquid intake has been described and is not different from the approved product information.

No immediate/acute AEs associated with the use of BLI800 (Eziclen®/Izinova®), in particular those indicative of electrolyte shift, was identified in special populations (i.e. the elderly and subjects at risk for electrolyte shifts). However, no firm conclusion can be drawn due to the small number of subjects identified in these populations at risk for electrolyte shifts, specifically renal and liver disease. Moreover, given that laboratory data were not routinely obtained in this non-interventional setting, the occurrence of subclinical laboratory changes not leading to clinical adverse events cannot be ruled out.

Marketing Authorisation Holder(s)

Ipsen Pharma SAS

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