Summary of Clinical Study Report

IV – Post authorisation safety study (PASS)

Study Title	A Multicentre, Non-interventional, Prospective, Observational Drug Utilisation Study of Ayendi Nasal Spray Prescribed as Treatment in Emergency Departments in the United Kingdom (UK)
Short Title and Identifier	DIAPASS (DIA003)
Final study report version and date	V1.0 04/11/2019
Reporting period	16/01/2017 – 27/03/2019
EU PAS register number	EUPAS15371
Active substance	Diamorphine (as Hydrochloride) ATC Code: N02AA09; Natural opium alkaloids
Medicinal product	Ayendi 720microgram/actuation Nasal Spray Ayendi 1600microgram/actuation Nasal Spray Ayendi will be supplied by hospital pharmacy (not by Sponsor) as part of routine ED practice.
Product reference	PL29831/0465 (720 mcg/ actuation); PL 29831/0466 (1600 mcg/ actuation)
Procedure number	Not applicable
Marketing authorisation holder(s)	Wockhardt UK Limited, Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF
Research question and objectives	The purpose of this prospective observational study is to evaluate the practical usage of the product as a treatment post authorisation.
Country(-ies) of study	UK
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Keywords

post marketing; analgesia; intranasal diamorphine; emergency; paediatric.

Rationale and background

On review of the marketing authorisation application for Ayendi Nasal Spray by MHRA, it was noted that the safety study (DIA002) highlighted difficulties of administering the product in the Emergency Department (ED). This post-authorisation safety study (PASS), DIA003, was requested by MHRA to evaluate the practical usage of the product as a treatment in the ED. The study assessed the patterns of use particularly in relation to aspects that may have an impact on the safety of the product (e.g. co-medication [including other opioids], medication errors). The study also assessed the effectiveness of risk minimisation activities.

Research question and objectives

To evaluate the practical usage of Ayendi Nasal Spray as a treatment post marketing in UK EDs.

The following information was collected and evaluated:

- Administration setting
- Patient characteristics
- Dose administered (to evaluate deviations from the prescribing and dosing instructions in the approved Summary of Product Characteristics)
- How prescribed and administered, (to evaluate if there are any differences in drug utilisation between the hospitals and prescribers)
- Adverse events
- Concomitant medication

The study assessed patterns of drug utilisation with respect to aspects that may have an impact on its safety (e.g. co-medication [including other opioids], medication errors) as well as evaluating the effectiveness of risk minimisation activities.

Study design

Observational Model: Case-Only

Time Perspective: Prospective.

Setting

UK EDs.

Subjects and study size, including dropouts

405 patients were recruited from EDs across 20 hospitals (from a wide variety with respect to teaching and non-teaching hospitals, geographical coverage across the UK, department size,

experience with diamorphine, and combined or separate paediatric EDs). Each site aimed to recruit a minimum of 10 patients and was limited to a maximum of 60 patients. The sample size had sufficient power to estimate both the rate of incorrect dosing and use in association with other opioids.

Study duration

The study opened on 11th January 2017, with first patient, first visit on the 16th January. The study recruitment completed on 27th March 2019 (last patient, last visit).

Variables and Data sources

Primary Parameters:

- Rate (%) of doses given (mg/kg) which deviate from the posology as written in the SmPC.
- Patients with previous opioid usage immediately prior to Ayendi (%)

Secondary Parameters:

- Time of administration (including pre-arrival at hospital, if appropriate)
- Dose Prescribed (mg/kg) vs Dose Given (mg/kg)
- Product strength and Number of sprays given
- Diagnosis for which Ayendi was prescribed (% used for off- label indications)
- Participating ED practice setting (%)
- Administrator (%)
- Concomitant medication
- Patient demographics (including patients who do not fit within the categories defined in the SmPC).
- Adverse events (%)

All patient data including AEs have been transcribed from ED records; Information not recorded as part of routine clinical practice has not been included in the CRF, even when available. The CRF is not regarded as primary source data.

ED administrator training data and administration setting were collected from study specific logs.

Safety Assessments:

Assessments of safety were performed throughout the time that the patient was in the hospital according to standard ED practice. No further data were collected regarding the patient once they left the ED.

Adverse events were defined as any new diagnosis, any reason for referral to a consultant (not related to the diagnosis for which the patient originally attended the ED), any unexpected deterioration in a concurrent illness, any suspected adverse drug reaction, or any complaint which was considered to be of sufficient importance such that it should be recorded in the patient's medical/nursing notes.

Results

405 patients have been included in all analyses. These patients are from 20 ED settings, across England and Scotland.

The results demonstrate that, although 41.2% of doses have deviated from the SmPC weight posology (12 kg -50 kg) and/or therapeutic indication overall age range (2-15 years old) and 2.7% of patients have been given previous opioids, the practical use of Ayendi in the ED is safe.

Seven mild adverse events and no SAEs were reported.

Discussion

These results demonstrated no safety concerns with the clinical use of Ayendi nasal spray in ED practice. Despite the fact that:

- dosing of 41.2% of patients deviated from the authorised SmPC weight posology and/or therapeutic indication overall age range (which decreases to 39.3% if only deviation from the weight posology is considered),
- 2.7% patients had received prior opioids, and
- 0.25% (1/403) of evaluable patients (403/405) were dosed for an indication not compliant with the SmPC (with 19.8% treated for an indication other than a fracture or a burn),

only seven adverse events have been reported (in four patients, none of whom had received any other opioids); all seven events were mild (with two considered unlikely to be related to Ayendi and five thought possibly related) and there were no Serious Adverse Events reported.

The Ayendi nasal device appears robust for use within the ED with only one possible medicine administration error (0.2%). Also, the prescribing error rate was only 0.7% (3 in 405 instances).

Thus, these data demonstrate the safe use of Ayendi in practice.