Post Authorisation Safety Study (PASS) to Evaluate the Risks of Hepatotoxicity and Nephrotoxicity from Administration of Methoxyflurane (Penthrox®) for Pain Relief in Hospital Accident & Emergency Departments in the United Kingdom (Penthrox-PASS)

First published: 05/04/2016

Last updated: 03/06/2026

Study Finalised

Administrative details

EU PAS number

EUPAS13040

Study ID

30864

DARWIN EU® study

No

Study countries

United Kingdom

Study description

Medical Developments UK Ltd (MDI) applied for marketing authorisation for a liquid inhalation preparation of methoxyflurane (Penthrox®) for the emergency relief of moderate-to-severe pain in conscious adult patients with trauma, through the decentralised procedure with the Medicines and Healthcare products Regulatory Agency (MHRA). Certain safety concerns, namely hepatotoxicity and nephrotoxicity, were identified by the MHRA medical assessor as potential public health risks. Consequently, a post-authorisation safety study (PASS), together with risk minimisation measures that are being evaluated separately from this study, was recommended. The primary purpose of the PASS is to confirm the absence of a significant risk of hepatotoxicity associated with the use of methoxyflurane in routine pre-hospital clinical practice and in hospital Accident and Emergency (A&E) departments.

Study status

Finalised

Research institutions and networks

Institutions

OXON Epidemiology

Spain

United Kingdom

First published: 06/12/2010

Last updated: 03/06/2026

Institution | Laboratory/Research/Testing facility | Non-Pharmaceutical company | ENCePP partner

Networks

NIHR Medicines for Children Research Network

First published: 01/02/2024

Last updated: 01/02/2024

Network

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Nawab Qizilbash

Primary lead investigator

Study timelines

Date when funding contract was signed
Actual: 05/01/2016

Study start date
Planned: 14/08/2016

Actual: 15/12/2016

Data analysis start date
Planned: 01/12/2019

Date of interim report, if expected
Planned: 15/02/2019

Date of final study report
Planned: 31/01/2020

Actual: 16/10/2020

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Medical Developments International

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Non-EU RMP only

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Combined primary data collection and secondary use of data

Study design:

Hybrid observational PASS combining a prospective methoxyflurane exposure cohort, a prospective concurrent analgesic comparator cohort, and a retrospective CPRD-HES historical cohort. Patients were followed for 12 weeks to assess hepatic and renal outcomes.

Main study objective:

To evaluate whether administration of methoxyflurane (Penthrox®) for the relief of moderate to severe trauma-related pain in routine clinical practice is associated with an increased risk of hepatotoxicity or nephrotoxicity compared with other commonly used analgesics in UK Accident & Emergency departments. Secondary objectives included assessing risk in specific patient subgroups, evaluating potential off-label use and overdose, and describing use in patients with relevant risk factors.

Study Design

Non-interventional study design

Cross-sectional

Study drug and medical condition

Medicinal product name

PENTHROX

Study drug International non-proprietary name (INN) or common name

METHOXYFLURANE

Anatomical Therapeutic Chemical (ATC) code

(N02BG09) methoxyflurane

methoxyflurane

Medical condition to be studied

Pain management

Hepatotoxicity

Population studied

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Study design details

Setting

The study was conducted in ten Accident & Emergency departments across the United Kingdom and used linked CPRD-HES databases to identify a historical comparator cohort. Eligible adult patients receiving methoxyflurane or standard analgesics for trauma-related pain were enrolled prospectively and followed for 12 weeks. Historical controls were selected from adults attending A&E with fractures during the 24 months before methoxyflurane launch in the UK.

Comparators

Patients receiving other routinely used analgesics for trauma-related pain, including Entonox®, NSAIDs, opiates and ketamine, as well as a historical non-concurrent cohort from CPRD-HES.

Outcomes

Primary outcomes were hepatic and renal events occurring within 12 weeks following methoxyflurane or comparator analgesic administration.

Data analysis plan

Incidence rates of hepatic and renal events were estimated using Poisson regression. Comparisons between cohorts were performed, factors associated with events were assessed using multivariable logistic regression, and event-free survival was evaluated using Kaplan–Meier methods.

Summary results

No excess risk of hepatic events was observed with methoxyflurane compared with other standard analgesics, and renal events were less frequent in methoxyflurane-treated patients. Most events were mild to moderate, and the study found no safety signal for methoxyflurane-related hepatotoxicity or nephrotoxicity.

Documents

Study publications

Qizilbash, N., Kataria, H., Jarman, H. et al. Real world safety of methoxyflura…

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Other

Data sources (types), other

Survey questionnaire

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No