ISRCTN59179622 https://doi.org/10.1186/ISRCTN59179622

Study to assess the active substance bioavailability (amount of the drug that reach the blood circulation), adhesion and tolerability of the medicated plaster Flector Unidie® applied once a day for 5 consecutive days to healthy volunteers

Submission date	Recruitment status	[_] Prospectively registered
20/10/2023	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
27/10/2023	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
12/09/2024	Other	

Plain English summary of protocol

Background and study aims
Flector Unidie® 14 mg is a well-known medicated plaster, which has been authorized and marketed in Italy for many years. The holder of the marketing authorization is IBSA Farmaceutici Italia Srl. The Sponsor has decided to investigate the bioavailability of piroxicam in plasma after cutaneous application of Flector Unidie® medicated plaster in healthy men and women, with the aim to generate data to be used as a reference for the future development of newly derived piroxicam-containing topical pharmaceutical products. The objective of this study is to investigate the pharmacokinetics of piroxicam after daily (24 hours) application of Flector Unidie® 14 mg medicated plaster to healthy volunteers for 5 consecutive days. Adhesion, local tolerability and safety of the investigational product will also be assessed.

Who can participate?
Healthy men and women, aged 18-55 years old

What does the study involve?
The medicated plaster will be applied each morning at 08:00 ± 1 h for 5 days, from Day 1 to Day 5, and kept in place for 24 h. The Investigator will select one arm of the subject on the basis of his /her individual characteristics (e.g., arms with tattoos or abrasions will be avoided) and will apply the plaster on the deltoid muscle, i.e., covering the shoulder and the top of the arm. If deemed necessary, on Day -1 the application site will be clipped (not shaved) and cleaned. During the study, blood samples will be collected from participants for the measurement of piroxicam in the bloodstream.

What are the possible benefits and risks of participating?
No specific benefits for the participants in the current study are foreseen. The participants will be reimbursed after study completion. The remuneration covers loss of time and any inconvenience caused by participation in the study.
Regarding the possible risks, many patients have been treated with Flector Unidie® 14 mg medicated plaster since its first registration in Italy. Flector Unidie® is under constant monitoring: no relevant risks related to its topical exposure have emerged. On the basis of the marketing experience, no potential risks are foreseen for the subjects enrolled in the present study. The more frequent side effects collected from post-marketing data concern skin reactions at the application site. Flector Unidie® can cause local irritation or allergic skin reactions such as erythema, itching, burning, contact dermatitis, numbness and tingling at the application site. Uncommon cases of extensive and severe skin lesions, such as urticaria, Quincke's oedema and erythema multiforme were reported. Photosensitivity reactions and more extensive and severe skin and mucosal reactions, including asthma attacks, were also observed. Systemic adverse reactions following the topical use of piroxicam are unlikely. However, since the plasma levels obtained are lower than those measured after systemic administration but vary greatly from person to person, the onset of systemic undesirable effects, especially of the gastrointestinal system, cannot be ruled out. The study involves blood samplings with cannula insertion, which may cause only minor discomfort. The risks associated with blood draws include pain, bleeding and bruising.

Where is the study run from?
IBSA Institut Biochimique S.A. (Switzerland)

When is the study starting and how long is it expected to run for?
June 2023 to November 2023

Who is funding the study?
IBSA Institut Biochimique S.A. (Switzerland)

Who is the main contact?
Mrs Serena Caverzasio, Jr. R&D Scientific Affairs Specialist, serena.caverzasio@ibsa.ch

Contact information

Type(s)
Public, Scientific

Contact name
Mrs Serena Caversazio

Contact details
Via Pian Scairolo 49
Pazzallo
Switzerland
6912
+41 58 360 10 00
serena.caverzasio@ibsa.ch

Type(s)
Scientific, Principal investigator

Contact name
Mr Milko Radicioni

Contact details
Via F.A. Giorgioli 14
Arzo
Switzerland
6864
+41 91 64 04 450
clinic@croalliance.com

Additional identifiers

Protocol serial number
23CH-Pxp04

Study information

Scientific Title
Bioavailability, adhesion and tolerability study for the evaluation of Flector Unidie® medicated plaster applied once a day for 5 consecutive days to healthy volunteers

Study objectives
To describe the pharmacokinetic profile of piroxicam after application of Flector Unidie® 14 mg medicated plaster once a day for 5 consecutive days

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 09/08/2023, Cantonal Ethics Committee Canton Ticino (c/o Health Office, Via Orico, 5, Bellinzona, CH-6501, Switzerland; +41918143057; beatrice.giberti-gai@ti.ch), ref: 2023-01396 Rif. CE 4425

Primary study design
Interventional

Study design
Single-centre repeated applications open-label pharmacokinetic adhesion and tolerability pilot study

Study type(s)
Other, Treatment, Safety

Health condition(s) or problem(s) studied
Evaluation of bioavailability, adhesion and tolerability of Flector Unidie® medicated plaster applied once a day for 5 consecutive days to healthy volunteers

Interventions

One (1) Flector Unidie® (piroxicam) 14 mg medicated plaster will be applied once a day (o.d.) for 5 consecutive days to healthy men and women. The medicated plaster will be applied each morning at 08:00±1 h for 5 days, from Day 1 to Day 5, and kept in place for 24 h.

The Investigator will select one arm of the subject on the basis of his/her individual characteristics (e.g., arms with tattoos or abrasions will be avoided) and will apply the plaster on the deltoid muscle, i.e., covering the shoulder and the top of the arm. If deemed necessary, on Day -1 the application site will be clipped (not shaved) and cleaned.

All the subjects enrolled in the study will receive the same treatment. No randomisation procedure will be applied.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Piroxicam

Primary outcome(s)
Plasma piroxicam concentration profile (drug absorption, distribution, metabolism and excretion) and pharmacokinetic parameters (Cmax0-24h, C24h, AUC0-24h, tmax0-24h, Cmin0-24h, Cave0-24h, Flu% [0-24h], AUC0-t, AUC0-72 and, if feasible, AUC0-inf, and t1/2) after the last repeated application of Flector Unidie® 14 mg medicated plaster. Plasma concentrations of piroxicam will be measured using a validated bioanalytical method on Days 1, 2, 3 and 4 at pre-application (0), on Day 5 at pre-application (0) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 16 h post-application (the collection at 16 h post-dose could take place on Day 6, it depends upon the IMP administration time), on Day 6 at 24 and 36 h post-application, on Day 7 at 48 h post-application and on Day 8 at 72 h post application.

In detail, the following pharmacokinetic parameters will be measured:
Cmax0-24h: maximum plasma concentration in the 24 h interval achieved after repeated applications; C24h: plasma concentration at the time-point of 24 h after repeated applications; AUC0-24h: area under the concentration-time curve in the 24 h interval, calculated with the linear trapezoidal method; tmax0-24 h: time to achieve Cmax0-24 h; Cmin0-24h: minimum plasma concentration in the 24 h interval achieved after repeated applications; Cave0-24h: average plasma concentration in the 24h interval achieved after repeated applications, calculated as AUC0-24h/0-24h; Flu%(0-24h): percentage of fluctuation, calculated as 100* (Cmax0-24h-Cmin0-24h)/Cave0-24h; AUC0-t: area under the concentration-time curve from administration to the last observed concentration time t, calculated with the linear trapezoidal method; AUC0-72: area under the concentration-time curve from administration to 72 h post-dose, calculated with the linear trapezoidal method; AUC0-inf: area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as AUC0-t + Ct/λz, where Ct is the last measurable drug concentration; t1/2: half-life, calculated, if feasible, as ln2/λz.

Key secondary outcome(s)
1. Adhesion scores and estimated percentage of adhered plaster area for Flector Unidie® 14 mg medicated plaster. Adhesion of the plaster will be evaluated at 4, 8, 12, 16 and 20 h post-application. The assessment will be performed using the following 5-point scale:

- 0 >= 90% adhered (essentially no lift off of the skin)
- 1 >= 75% to < 90% adhered (only some edges of the plaster lift off the skin)
- 2 >= 50% to < 75% adhered (less than half of the plaster lifts off the skin)
- 3 > 0% to < 50% adhered (the plaster is not detached, but more than half of the plaster lifts off the skin without falling off)
- 4 0% adhered (the plaster is detached and is completely off the skin).
In addition, at each time point, the actual percentage adhesion value (%) will be estimated by the Investigator.
2. Treatment-emergent adverse events during the study
3. Vital signs (blood pressure, heart rate) measured at the screening visit, on Day 7 at 48 h post-application (before discharge) and at the final visit/ETV
4. Local tolerability, assessed by the Investigator at the application site before the first plasters application on Day 1 (pre-application) and after plasters removal on Days 2, 3, 4, 5 and 6. Local tolerability will be assessed by giving a score to each of the tolerability parameters (application site erythema, application site dryness, application site swelling and application site exfoliation) according to a 4-grade scale (0 None, 1 Mild, 2 Moderate, 3 Severe)
5. Physical examination (including body weight) at screening and final visit/ETV
6. Laboratory parameters at screening and final visit/ETV.

Completion date
08/11/2023

Eligibility

Key inclusion criteria
1. Informed consent: signed written informed consent before inclusion in the study
2. Sex and Age: men/women, 18-55 years old inclusive
3. Body Mass Index (BMI): 18.5-30 kg/m2 inclusive
4. Vital signs: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-99 bpm, measured after 5 min at rest in the sitting position
5. Full comprehension: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to cooperate with the Investigator and to comply with the requirements of the entire study
6. Contraception and fertility (women only): women of child-bearing potential must be using at least one of the following reliable methods of contraception:
6.1. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit
6.2. A non-hormonal intrauterine device (IUD) or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
6.3. A male sexual partner who agrees to use a male condom with spermicide
6.4. A sterile sexual partner.
or:
True abstinence (i.e., refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), lactational amenorrhea, and withdrawal are not acceptable.
Women of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted. For all women, pregnancy test result must be negative at screening and Day -1.

Participant type(s)

Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Total final enrolment
12

Key exclusion criteria
1. Electrocardiogram (ECG) 12-leads (supine position): clinically significant abnormalities
2. Physical findings: clinically significant abnormal physical findings which could interfere with the objectives of the study
3. Laboratory analyses: clinically significant abnormal laboratory values indicative of physical illness
4. Application site: diseased skin, skin wounds, open injuries or tattoos on both deltoid muscles or any other physical/medical condition which could interfere with the objectives of the study
5. Allergy: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study
6. Diseases: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study
7. Medications: medications, including over-the-counter (OTC) medications (in particular, non-steroidal anti-inflammatory drugs) and herbal remedies, for 2 weeks before the start of the study. Hormonal contraceptives for women will be allowed
8. Investigative drug studies: participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study
9. Blood donation: blood donations for 3 months before this study
10. Drug, alcohol, caffeine, tobacco: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025 (18)], caffeine (>5 cups coffee/tea/day) or tobacco abuse (10 cigarettes/day)
11. SARS-CoV-2 test: positive COVID-19 rapid test at screening or Day -1
12. Drug test: positive result at the drug test at screening or Day -1
13. Alcohol test: positive alcohol saliva test at screening or Day -1
14. Diet: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the

4 weeks before this study; vegetarians and vegans
15. Pregnancy (women only): positive or missing pregnancy test at screening or Day -1, pregnant or lactating women.

Date of first enrolment
24/10/2023

Date of final enrolment
27/10/2023

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research S.A. Phase I Unit
Via F.A. Giorgioli 14
Arzo
Switzerland
6864

Sponsor information

Organisation
IBSA Institut Biochimique (Switzerland)

ROR
https://ror.org/051tj3a26

Funder(s)

Funder type
Industry

Funder Name
IBSA Institut Biochimique S.A.

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to reasons linked to a patent process.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		11/09/2024	12/09/2024	No	No