Safety of ibuprofen after major orthopaedic surgeries

A protocol for the PERISAFE randomized clinical multicentre trial

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Abstract

Trial name: safety of ibuprofen after major orthopaedic surgeries. The PERISAFE randomized clinical multicentre trial

Trial acronym: PERISAFE

Background: hip and knee arthroplasty surgeries are some of the most frequently performed planned surgical procedures in the western world. Multimodal analgesic treatment is the leading principle to treat acute postoperative pain, with non-steroid anti-inflammatory drugs (NSAIDs) as an essential part. Ibuprofen, the most prescribed NSAID, is effective in reducing acute postoperative pain. However, ibuprofen may be associated with various serious adverse events, including death, cardiovascular morbidity, gastrointestinal ulcer, and renal impairment. The balance between beneficial and harmful effects of a short-term postoperative treatment with ibuprofen after elective hip and knee arthroplasty surgery remains unknown.

Objective: the primary objective of this trial is to assess the beneficial and harmful effects of an eight-day postoperative treatment with ibuprofen in patients undergoing elective hip or knee arthroplasty surgery.

Intervention: the patients will be randomized into two groups:

1. Ibuprofen 400 mg tablet, x3 per day for eight days after surgery.
2. Placebo, identical tablet, x3 per day for eight days after surgery.

Design and trial size: PERISAFE is a randomized, placebo-controlled multicentre trial with adequate centralized computer-generated allocation sequence and allocation concealment with unknown block size. Patients, investigators, assessors, caregivers, data-managers, writers of the manuscript, and statisticians will be blinded. A total of 2904 eligible patients are needed to detect or discard an effect corresponding to a relative risk reduction of 33%, a proportion of the composite outcome of serious adverse events of 8% in the ibuprofen group, and accepting a risk of type I error of 5 % and of type II error of 20%.

Inclusion criteria: patients scheduled for planned primary hip and knee arthroplasty; age ≥ 18 years; planned perioperative treatment with NSAID; negative HCG-pregnancy test for women in the fertile age; informed consent.

Exclusion criteria: unable to understand or speak Danish; allergy to, or contraindications against ibuprofen.

Primary outcome: a composite outcome of either death, acute myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, renal failure, major bleeding, re-operation, gastrointestinal ulcer, or readmission within 90 days postoperatively.

Secondary outcome: hospital free days within 90 days postoperatively; a composite outcome of ibuprofen related adverse events (pain or discomfort from the epigastrium, reflux, diarrhoea)

based on eight-day postoperative diary; a composite outcome of opioid related adverse events (nausea, vomiting, constipation, sedation, headache, mood changes, mouth dryness) based on eight-day postoperative diary; and health related quality of life questionnaire (EQ-5D-5L) after 90 days.

Exploratory outcomes: proportion of individual serious adverse events in the composite primary outcome; proportion of individual adverse events of ibuprofen and opioid in the composite secondary outcomes; postoperative pain levels, analgesic treatment, and opioid consumption based on eight -day postoperative diary and on a questionnaire 14 days postoperatively.

Sub-studies: one-year follow-up on the composite primary outcome. Furthermore, we plan a subgroup analysis on predictors of chronic pain and opioid consumption at 90-days, and one-year after surgery. Additional, we plan to investigate the coherence of preoperative use of diuretics, ACE-inhibitors or angiotensin-II-antagonists and postoperative risk of renal failure.

Time Schedule: we plan to start enrolment from April 1st 2023 and expect to finish December 2026. Data analysis will be conducted primo 2026 and the manuscript submitted ultimo 2026.

General information and signature page

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List of abbreviation

CI	Confidence Interval
COX	Cyclooxygenase
CRF	Case Report Form
DMSC	Data Monitoring and Safety Committee
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
NSAID	Non-steroid Anti-inflammatory Drug
NNT	Number Needed to Treat
SUSAR	Suspected Unexpected Serious Adverse Reaction

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1 Background

1.1 Description of the condition

Hip and knee arthroplasties

More than 300 million operations are performed worldwide per year.[1] Hip and knee arthroplasty surgeries are some of the most frequently performed planned surgical procedures in the western world, and are acknowledged to improve pain, quality of life, and functional status in patients suffering from severe osteoarthritis.[2] Worldwide, more than 1.5 million total hip and knee arthroplasty procedures are performed annually and the number is increasing.[3–6] From 2020 to 2021, 10,834 hip- and 10,496 knee arthroplasties were performed in Denmark.[7,8]

Risk of adverse events following surgery

The reported overall 30-day non-cardiac surgical mortality rate is around 2.0%[9] with almost 27% of these dying after hospital discharge.[9,10] In Denmark, approximately two million surgical procedures are performed annually,[11] with reported mortality rates of 2-3% and 4-6% at 90- and 180-days, respectively.[9,12,13] This corresponds to over 40,000-80,000 surgical-related deaths per year. A recent Danish registry study[12] of 7,449 adult patients from different surgical specialties found a risk of a composite outcomes of death, myocardial infarction, pulmonary embolism, stroke, gastrointestinal bleeding, dialysis, or reoperation of 8.3% in a 342-day postoperative follow-up period. Of these, 2.35% were in elective orthopaedic patients.

Hip and knee arthroplasty surgeries are generally acknowledged as safe, with a 90-day mortality rate of 0.5% and 0.4% for total hip and knee arthroplasties, respectively.[14] However, older age, multimorbidity and prior cardiac disease is associated with higher 90-day mortality.[14] A recent cohort study [15] of 36,935 total hip and knee arthroplasty patients viewed a decline in overall length of stay from three days in 2010 to one day in 2017. However, although the 90-day readmission rate also declined in the period, it was still 7.7%. This was supported by a Swedish observational study[16] of 14,148 hip and knee arthroplasty surgeries that found a 90-day readmission rate of 7.2% and 8.4% after total hip and knee arthroplasties, respectively.[16]

1.2 Description of the intervention

Postoperative pain

Acute postoperative pain is a combination of local and systemic pain responses caused by the surgical trauma.[17,18] The nociceptors distributed in the skin, muscles and joints are stimulated by noxious stimuli. Further, the surgical trauma leads to activation and sensitization of the nociceptive system through release of different mediators: bradykinin, prostanoids (thromboxane A_2, prostacyclin, prostaglandin D_2, E_2, F_2), and cytokines. The activated cytokines and prostanoids, especially prostaglandin E_2 and I_2, are involved in peripheral and central sensitization and in neuro-inflammatory pain.[19] The stimuli are transduced and transmitted to the central nervous system via afferent Aδ and C nerves fibres to the dorsal horn of the spinal cord and further to the somatosensory cortex.[20]

The surgical stress response plays an important role for postoperative pain mechanisms[21] and includes inflammatory components that affect the postoperative recovery.[22,23] It leads to activation of both pro- and anti-inflammatory components and induce activation of the neuroendocrine system.[24] Therefore, the surgical stress response both initiates a local and systemic response, increasing pain, nausea, vomiting, and cerebral dysfunction.[22,24] The systemic inflammatory response is associated with postoperative morbidity, and with a higher risk of infection and organ failure.[24] Therefore, surgical stress may increase the length of hospitalization and delay discharge.[21] Additionally, it is related to perioperative cardiac complications for patients undergoing major non-cardiac surgery.[9]

Postoperative pain management

Multimodal analgesic treatment is considered the current leading treatment principle for managing acute postoperative pain, with combinations of basic non-opioid analgesics, local anaesthetics, glucocorticoids and opioids as needed.[21,25–28] It is recommended by the American Society of Anaesthesiologist guidelines and Enhanced Recovery After Surgery protocols in the perioperative period, [28,29] with basic non-opioid analgesics consisting of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).[28] Poorly controlled acute postoperative pain may result in immunosuppression, and increased cardiorespiratory work, and catabolism.[17] Further, it may lead to prolonged recovery.[17] Therefore, effective postoperative pain management is essential both for the well-being of surgical patients and to facilitate rehabilitation without inducing harm.[24,29–31]

With increased focus on early rehabilitation with effective postoperative pain management and opioid-sparing analgesics; paracetamol and NSAIDs plays an important role for postoperative analgesic treatment.[28,29,32] Both drugs are commonly used with proven analgesic efficacy when administrated alone.[25,33] However, combinations of paracetamol and NSAIDs has shown to decrease opioid consumption, pain levels, and opioid related adverse events postoperatively, compared to patients receiving either drug alone. [31,34] Furthermore, routine use of NSAIDs is a part of World Health Organization's pain relief ladder.[31,35–37]

Pain after hip and knee arthroplasties are moderate to severe, but no golden standard for pain treatment is available in the literature.[38,39] Although Enhanced Recovery After Surgery and other guidelines recommend treatments with both paracetamol and NSAIDs for these procedures,[28,29,31] there is no consensus on type of NSAIDs, treatment regime, and length of treatments. These choices are left to the individual orthopaedic or local orthopaedic guidelines.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are antipyretic, anti-inflammatory, and analgesic agents.[40] They are frequently prescribed drugs globally. In the United States alone, more than 70 million prescriptions were dispensed in 2017 with ibuprofen accounting for the most commonly prescribed NSAID with 44.8 million prescriptions.[34] Additionally, an estimated number of 172 million packages of ibuprofen products were sold 'over-the-counter' the same year with increasing trends from 2006 to 2017.[34]

Between 1997 and 2005, 57.8% of the Danish population claimed at least one prescription for NSAID. The most common NSAID prescription was ibuprofen, with increasing use in the period. NSAIDs were often prescribed for use for a specific treatment interval or short period and did not differ between ages.[41]

Ibuprofen

Ibuprofen is a non-selective NSAID and is the most used NSAID worldwide.[41,42] Further, it is available in many countries as over-the-counter drug in varying doses.[34,41] A recent national survey of NSAID use at all Danish Orthopaedic Departments confirmed ibuprofen, as the most common NSAID prescribed postoperatively after elective hip (77.8%) and knee (66.7%) arthroplasties (own data, not published yet).

Ibuprofen has been shown to reduce pain and opioid consumption postoperatively,[25,31,43] and is widely used at the different surgical departments.[29] It is a standardized part of the postoperative analgesic treatment after major orthopaedic surgeries.[29] However, in non-surgical populations, treatment with ibuprofen in varying doses and treatment length has been associated with several adverse events, including gastrointestinal bleeding,[44,45] renal failure,[46] cardiovascular mortality and morbidity.[42,45]

1.3 How the intervention might work

Mechanism of action

NSAIDs are generally divided into two main isozymes based on their chemical structure and selectivity: non-selective (effect on both selective cyclooxygenase (COX)-1 and COX-2 receptors, e.g., ibuprofen, naproxen, diclofenac, ketorolac), and COX-2 selective inhibitors (e.g., etoricoxib, celecoxib).[47] COX-1 is constitutively expressed in the body and is upregulated during the inflammatory response. COX-1 affect the gastrointestinal mucosa lining, renal function, and platelet aggregation. COX-2 is inducible expressed during inflammatory response. COX-2 affects among other the bone formation, renal function, mitogenesis and growth, and regulation of female reproduction.[40,47,48] Both COX isozymes is expressed in endothelial cells.[49]

The main mechanism of NSAIDs is inhibition of the enzyme COX, which is required to convert arachnoid acid into prostaglandin G_2 and H_2. Prostaglandin H_2 are further converted into prostanoids, including thromboxane A_2, prostacyclin and prostaglandin D_2, E_2 and F_2 via tissue-specific isomerases.[50] Thromboxane A_2, prostacyclin and prostaglandin E_2 affect the platelet aggregation, whereas the other prostaglandins affect regulation of renal blood flow, regulation of endothelial tone, and maintenance of gastric mucosal barrier.[50,51] In addition, prostaglandins increase the temperature set point in the hypothalamus and affect both the peripheral and central nociception.[47,50,52] The peripheral nociceptors ascending pathway are affected by the inhibition of prostaglandin synthesis, thereby preventing sensitization of pain receptors in response to the mechanism injury.[52] Additionally, the inhibition of prostaglandin E_2 in the spinal dorsal horn

activates the medullary and cortical regions in the central nervous system, resulting in central sensitization and lower pain threshold in the surrounding uninjured tissue.[52]

Effects on acute pain and rehabilitation

NSAIDs have shown to be effective in reducing acute postoperative pain.[25,27,29,31,53] They alleviate pain by reducing the inflammatory response caused by tissue damage, and by preventing peripheral and central sensitization. A previous study [35] of pain prophylaxis found NSAID to reduce morphine consumption by 9.45 mg (95% confidence interval (CI) [8.01-10.90]) compared to placebo during the first 24-hours after major surgery.[35] Furthermore, a recent randomized clinical trial[31] found the combination of paracetamol 4 g/day and ibuprofen 1600 mg/day to reduce morphine consumption with 16 mg/24h compared with paracetamol alone after elective total hip arthroplasty surgery. Further, the combination also reduced opioid consumption compared to ibuprofen alone.[31]

Additionally, NSAIDs have been associated with improved short-term postoperative rehabilitation,[24,30] and their anti-inflammatory effects may be important for other post-surgical outcomes by reducing the surgical stress response.[24,53,54]

Adverse events of NSAIDs

Gastrointestinal adverse events

Thromboxane-synthesis in the ventricle provides protection against the effect of stomach acid on the upper gastrointestinal mucosa and is inhibited by NSAIDs.[48] Furthermore, NSAIDs has a direct toxic effect on the gastroduodenal mucosa and also indirectly affect active hepatic metabolites which is excreted into the bile and afterwards into duodenum where they may cause mucosal damage to the stomach by duodenal-gastric reflux, and mucosal damage to the small intestine by anterograde passage through the gastrointestinal tract.[48]

Renal impairment and blood pressure

The effect on both COX-1 and COX-2 isozymes inhibits the prostaglandin synthesis, which play an important role for renal function through regulation of a variety of physiological processes.[55] The renal function is affected by regulation of sodium and chloride transport, the modulation of water transport and renal medullary blood flow. Furthermore, prostaglandins increase the potassium secretion mainly by stimulating the secretion of renin and activation of the renin-angiotensin-aldosterone system.[55] Additionally, the renal vascular tone, glomerular filtration rate and renin release is regulated by prostaglandins. [55]

Postoperative bleeding

The inhibition of thromboxane A_2 formation by NSAIDs may increase the risk of surgical related bleeding.[43,56]

Cardiovascular and cerebrovascular adverse events

NSAIDs have been associated with risk of cardiovascular serious adverse events, including cardiovascular death, myocardial infarction, and stroke.[45,57–60] However, the risk differs among

types of NSAIDs and COX-2 affinity.[42,57,61] Theoretically, the imbalance between prostacyclin and thromboxane A_2 may lead to increased risk of thrombotic events.[57] This is supported the hypothesis of COX-2 inhibition shifting the antithrombotic balance to be prothrombotic, mainly by inhibition of the prostacyclin synthesis, which inhibits the platelets aggregation.[62] COX-2 inhibitors have been related with high risks of cardiovascular morbidity and mortality,[63,64] which resulted in the withdrawal of rofecoxib in 2004.[63,64]

Impaired bone healing and prosthetic loosening

Impaired bone healing has been a concern since experimental animal data suggested a correlation of NSAID and delayed bone healing.[65] However, the concern appears to be controversial, and the literature is inconclusive.[65] Theoretically, both COX isozymes promote the synthesis of prostaglandin E_2 which increases the number of active osteoclasts and stimulate the bone formation by increasing the replication and differentiation of osteoblasts. Furthermore, by increasing the blood supply to the site, which leads to increased angiogenesis.[66]

Adverse events of opioids

Opioids are frequently prescribed drugs and are a mainstay of the postoperative multimodal analgesic regime.[28,29] However, they are associated with a variety of serious and non-serious adverse events, including respiratory depression, nausea, vomiting, constipation, dizziness, confusion, sedation, and headache, which may lead to prolonged hospitalization.[67–69] The adverse events of opioid treatment are most likely dose dependent, and is more often seen with intravenous administration after major surgery.[67,68] There has been a general focus of decreasing the opioid consumption in order to reduce harm, therefore recommending multimodal analgesic treatment with basic non-opioids; e.g. paracetamol and NSAIDs.[25]

1.4 Why it is important to do this clinical trial

A 2009 Cochrane review [70] found that a single dose of oral ibuprofen of 400 mg had a number needed to treat (NNT) of 2.5 (95% CI 2.4-2.6) in patients of mixed type surgery and with moderate pain to achieve at least 50% pain relief. The included trials however, collected adverse events the first four to eight hours, a few up to 24 hours, and only one trial up to 14 days. Adverse events were mild and not increased with ibuprofen.

The general research focus in the pain literature is on efficiency data, whereas safety data are in short supply (Appendix 1 and 2), and the role of analgesic treatment for the risk of serious adverse events remain generally unknown.[38,43] Previous efficiency studies are of varying types of NSAID intervention, length of treatment, and mostly with short-time follow-up. [43]

General evidence on adverse events of NSAIDs when used in mixed patient population

Apart from NSAIDs well-known pain-relieving abilities, NSAIDs have been associated with a variety of serious adverse events, including gastrointestinal ulcers,[71,72] bleeding,[71,72] kidney impairment,[10] and cardiovascular morbidity and mortality in primarily non-surgical patients.[73–75]

Gastrointestinal serious adverse events have been associated with high dosage and long term NSAID treatment in previous reviews of mixed patient population.[43,48,72] Additionally, patients with history of gastroduodenal or gastrointestinal bleeding, concomitant use of corticosteroids and concomitant use of anticoagulants were with increased risk.[48]

The influence of NSAID treatment on postoperative renal function is not established in the literature.[10,43] A recent Cochrane review found uncertain evidence regarding the association between perioperative NSAID treatment and risk of acute postoperative renal failure due to heterogeneity between the studies and high risk of bias of the majority of the trials included.[10] Though, elderly patients with preoperative reduced kidney function and patients with perioperative low blood pressure treated with NSAID perioperative, may have increased risk of acute kidney failure.[46,55,76]

A systematic review from 2021 did not find NSAID to be associated with postoperative bleeding complications with varying types of NSAIDs in mixed surgical population.[77] However, short time treatment (zero to three days) with NSAIDs in patients receiving antithrombotic therapy after myocardial infarction may be related to increased risk of postoperative bleeding. [61]

Both reviews,[57,62,78] randomised clinical trials,[45,63,64] and large observational studies[59,60] have found non-selective NSAIDs and COX-2 inhibitors to be associated with increased cardiovascular morbidity and mortality. The risk appears to be dose- and duration dependent. However, the results are primarily from retrospective studies and from few randomised trials; two of COX-2 inhibitors[63,64] and one of long-term treatment (celecoxib, naproxen or ibuprofen) in moderate to high doses (1800-2400 mg/day of ibuprofen).[45]

A topical review of reviews on adverse events of non-opioid analgesics for postoperative pain, including NSAID[43] concluded that although previous meta-analysis and randomized clinical trials did not raise concern of the effect of NSAID on overall mortality, cardiovascular events, surgical bleeding or renal impairment in patients with normal kidney function prior to surgery, these results suffered from small sized trials investigating analgesic efficacy of short-term treatment, with short follow up period and were not powered to investigate harm. Further trials should focus on longer term follow up on harm to assess overall safety.

Previous evidence on the adverse events of NSAIDs in orthopaedic surgery

Systematic reviews

A limited number of reviews on NSAIDs have been made in orthopaedic patients (Appendix 1), and only few of these included trials of ibuprofen. No reviews have solely investigated efficacy and safety of ibuprofen in orthopaedic patients.

Reviews on effects of perioperative NSAIDs in orthopaedic patients have primarily focused on tissue or bone healing, and not overall safety (Appendix 1). Furthermore, not all reviews accounted for systematic errors (bias), random errors (trial sequential analyses), and only one review rated certainty of evidence by using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Randomized trials

Few randomized trials have investigated ibuprofen in orthopaedic patients (Appendix 2) and used varying daily doses from 1200 mg/day to 2400 mg/day, had intervention periods from 24 hours to 5 days, and overall with short time follow-up.

A recent randomized trial[31] found an insignificant, but numerically raised relative risk of 1.44 for serious adverse events after 24 hours treatment with ibuprofen of 1600 mg/day after elective total hip arthroplasty surgery between ibuprofen alone and paracetamol alone. The trial may however be underpowered (type II error) on this matter, and also no restriction was placed on analgesic use after the 24-hour intervention period and the 90-day follow-up, making attribution of serious adverse events to ibuprofen difficult.[31]

Appendix 2 show all randomized clinical trials investigating effects of NSAID in orthopaedic patients. The primary focus of these trials was most often on analgesic efficacy (pain and opioid sparing) investigating different types of interventions and treatments from a single dose to three weeks treatment, but generally with short-time follow-up and with sparse focus on specific adverse events. Furthermore, these trials were not powered to investigate safety or harm in general.

1.5 Dose and duration of treatment of ibuprofen

European Medicines Agency generally recommends the lowest dose and shortest time of duration of treatment as possible, and with ibuprofen at doses of $\leq$ 1200 mg/day based on data from cohort studies.[79,80] They state that such dose of ibuprofen are likely not related to increased cardiovascular risk, and that benefits overweight the possible risk.[79] Further, the European Medicines Agency states that there is a small increased cardiovascular risk with daily doses at or above 2400 mg, and recommends that doses > 1200 mg per day should be avoided in patients with increased risk of cardiovascular events.[79]

Overall, the recommendation of ibuprofen from the European Medicines Agency is based on reviews, meta-analysis, cohort studies, and few randomizes trials of medical patients.[79,80] The risks of serious adverse events in the surgical patient population lacks to be investigated in sufficiently powered randomized trials.[12,43]

It has been established that the association of NSAID treatment and risk of adverse events are dose- and treatment duration dependent.[42,44–46,60,73] However, short-time treatment may be safe.[42,73] A previous cohort study [42] investigating the risk of death or re-myocardial infarction in patients with prior myocardial infarct suggested that a short-time treatment (seven-days) with ibuprofen may be safe. This was confirmed by an observational study of short-time postoperative treatment with NSAIDs in total hip and knee arthroplasty patients.[81] Overall, certain relationship between ibuprofen and cardiac adverse events in surgical patients lacks in the literature.[12,43]

A recent Danish National survey (own data, not published yes) at all Danish Orthopaedic departments found a noteworthy difference between duration of postoperative analgesic

treatment with NSAID after elective total hip and knee arthroplasties from three to thirty days, with a median of eleven days. This demonstrates that current clinical practise lacks evidence based guidelines on treatment duration.

2 Trial objectives and purposes

We aim to assess the beneficial and harmful effects of an eight day postoperative treatment with ibuprofen, a non-selective NSAID and one of the most used non-opioid analgesics, after elective hip and knee arthroplasties. We expect the results from this trial to establish better evidence for the safety of postoperative analgesic treatment with NSAID for patients undergoing such surgeries.

We hypothesize that in patients undergoing elective primary hip and knee arthroplasty surgeries, postoperative analgesic treatment without ibuprofen decreases the risk of serious adverse events within 90 days postoperatively.

We therefore expect the results to have major impact on treatment of orthopaedic surgical patients in the future and be a cornerstone in the guidance of clinicians for decisions on perioperative pain treatment.

3 Trial design

We plan a superiority, investigator initiated, randomised, placebo-controlled, blinded, multicentre clinical trial randomising 2904 participants scheduled for hip and knee arthroplasty to either tablet ibuprofen 400 mg 3x per day or tablet placebo (identical) 3x per day for eight days postoperatively with follow-up 90 days postoperatively.

3.1 Trial conduct

The trial will be conducted in accordance with the principles of the Declaration of Helsinki and according to a SPIRIT compliant protocol approved by the competent authority and ethics committee, and according to Good Clinical Practice (GCP) standards.[82] No deviation from the protocol will be implemented without the prior review and approval of the regulatory authorities, except where it may be necessary to eliminate an immediate hazard to the trial patients. In such case, the deviation will be reported to the regulatory authorities as soon as possible. The trial design, status, and results will be reported in the international database www.clinicaltrials.gov and http://www.clinicaltrialregister.eu (CTIS).

3.2 Time schedule

The trial is scheduled to start 1st of April 2023 and is expected to be completed on 31 of December 2026 when the last patient enrolled has completed one-year follow-up (last contact to the patient). We will allow one month response time for the one-year follow-up.

3.3 Duration

Participating in this trial will not prolong admission or require extra follow-up visits. See section 6 “Trial intervention”.

4 Selection of participants

4.1 Inclusion criteria

Patients meeting all the following criteria are eligible for inclusion in the trial:

- Scheduled for planned primary hip or knee arthroplasty, including hemiarthroplasty.
- Age ≥ 18 years.
- Planned perioperative pain treatment with NSAID, decided by the clinical doctor.
- Negative urine Human Chorionic Gonadotropin (hCG) pregnancy test and use of anti-conception* for women in fertile age.
- Written informed consent.

*Approved anti-conceptions may be: combined estrogen and progestreron hormonal contraception, progesterone-only contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence.

4.2 Exclusion criteria

Patients meeting one or more of the following criteria are not suitable for inclusion in this trial:

- Patients unable to understand or speak Danish.
- Allergy to, or contraindications against ibuprofen, including heart insufficient (NYHA IV), severe thrombocytopenia (< 50 x 10^9/l), asthma triggered by NSAID, known renal impairment (eGFR < 60 ml/min), or previous ulcer due to NSAID treatment.

4.3 Screening

All patients scheduled for hip or knee arthroplasty will be pre-screened for the following in- and exclusion criteria:

- Scheduled for planned primary hip or knee arthroplasty, including hemiarthroplasty.
- Age ≥ 18 years.
- Planned perioperative pain treatment with NSAID
- Danish language comprehension
- Allergy to, or contraindications against ibuprofen

The investigators will obtain the pre-screening information from the patients' medical record. However, the final assessment of language comprehension, allergies to, or contraindications against ibuprofen will be obtained during the interview with the patient during obtaining of the informed consent.

After obtaining the informed consent, the patients will be screened for:

- Negative urine hCG pregnancy test and use of anti-conception for women in fertile age.

5 Participant withdrawal

A patient who has not completed the trial, is a patient included in the trial, i.e., who has given informed consent and been randomized, but withdraws consent and does not allow for continued data recording after discontinuing the trial medications.

If a patient does not complete the trial, an account should be given as to whether and how this patient is followed in the trial – this also applies to drop-outs – as well as what data has been collected from these patients.

5.1 Reasons for participant withdrawal from the trial

A patient can be withdrawn from the trial under the following conditions:

- If the investigator believes that a change of treatment will be best for the patient.
- If the patient wishes to withdraw from the trial.

5.2 Procedure for participants who withdraw from the trial

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the trial at any time and for any reason. The investigators also have the right to withdraw a patient from the trial at any time.

The reason why a patient is withdrawn from the trial before the scheduled time shall be recorded in the patient's worksheet or electronic Case Report Form (eCRF). However, the patient are not obliged to provide reason for withdrawn.

The patient will be asked if the withdrawal is only for the intervention/treatment and if he or she allows for further data registration or if withdrawal is for any further data registration as well.

5.3 Discontinuation of individual participants

If a serious adverse event occurs under admission, according to the International Conference on Harmonisation-GCP (ICH-GCP) definition, see section 9.1 "Safety variables and definitions", during intervention period, and the investigator, after consultation with either principal investigator or sponsor, finds it not feasible for the patient to continue, the patient will be discontinued and the patient will be asked whether we still can record data or not. Information on data is elaborated in section 7.5 "Data collection".

Emergency unblinding

The blinding may only be broken if the continued treatment of the patient requires knowledge of the randomization code due to safety. This can be done by the local investigator without restrictions. Breaking of the code can be done locally by accessing the sealed and opaque envelope of the investigator or by local clinicians. Every site will have a procedure for emergency unblinding described in detail. In case of emergency unblinding, date and reason must be recorded.

The investigator will ensure that necessary procedures and expertise is available to handle any emergency situations that may arise during the trial. Discontinued participants will not be replaced.

6 Trial interventions

The intervention period is from postoperative day 0 to postoperative day 7. One of the following interventions will be assigned to the participants:

- Tablet ibuprofen 400 mg 3x per day for eight days postoperatively.
- Tablet placebo (identical) 3x per day for eight days postoperatively.

The trial intervention period will begin in the afternoon or evening on the day of surgery (day 0) approximate eight hours after premedication (depending of type of NSAID given as premedication), and will continue the following seven days. The follow-up period is from randomization at postoperative day 0 to postoperative day 90.

In this trial, the dose of ibuprofen (1200 mg/day), and treatment length of eight days is a common analgesic regimen at Danish Orthopaedic departments.[59,60,73,78–80] Furthermore, the treatment is based on a recent, yet unpublished data of a national survey at all Danish departments of Orthopaedics.

According to the product summary, the most common adverse effects of ibuprofen is elaborated in table 1 below. All adverse effects of ibuprofen is elaborated in the product summary of "Ibumetin" in Appendix 3.

Table 1: Common adverse effects of ibuprofen 400 mg

Organ system	**Symptoms**	**Frequency**
Gastrointestinal system	Dyspepsia, Diarrhoea	≥10%
	Gastrointestinal bleeding, hematemesis, melena, abdominal pain, flatus	≥1%
Outer and inner ear	Tinnitus	≥1-0,1%
General symptoms	Fatigue	≥1%

6.1 Concomitant medication/treatment

Further analgesic treatment methods according to local standards, including escape medication, to ensure postoperative pain control, except use of unblinded NSAIDs, are allowed in the intervention period.

6.2 Monitoring for participant compliance

Patients will receive one package with the trial medication. Trial medication will be self-administered during admission. During admission and after discharge, compliance will be recorded by the patients in the eight-day diary during the intervention period. The diary will primarily be electronic. However, if the patients wish to receive the diary in paper-format, this will be complied with. A Central Unit will receive the paper diary and will enter the response into the eCRF (please view section 7.6 "Follow-up").

6.3 Intervention accountability

Intervention accountability will be ensured by the patients. Patients will self-administer the trial medication and will be informed properly about how to handle the self-administration. Administration will be registered in the eight-day diary.

Extradition of trial medication at the start of the intervention period (postoperative day 0) will be double-controlled by authorized personal, and registered in the eCRF with initials, allocation number, and batch number.

The investigators will perform a receipt check, when receiving a medication delivery. The check will ensure that the drug's storage conditions have been complied with during shipment, that the documentation required by this notice is included and that the delivered drugs are in compliance with the ordered.

The investigators will ensure that the trial medication is kept in a safe place and only provided to patients in this trial. The investigator will ensure that there is strict accounting of the trial medication supplied. The investigator shall give an account of any medication that accidentally or otherwise gone missing, and for any discrepancy between the supplied and returned medications to the pharmacy.

6.4 Randomization

Patients will be randomized into two groups in a 1:1 ratio with a varying block size of either 4, 6, or 8 in overall chunks of 24 (unknown to the investigators). The randomization will be performed by the Copenhagen Trial Unit via central computer-generated allocation, which will export the allocation numbers to Redcap – clinical trial management. Randomization will be stratified for site. The pharmacy will supply the trial medication in package with identical tablets making distinction between active and placebo intervention impossible. Medication will be packed and labelled according to the allocation numbers. The pharmacy will produce two sets of sealed, opaque envelopes. These will contain information on which treatment the individual participant is randomized to. One set is stored by the sponsor in a locked cabinet. The other set is stored in a locked local cabinet, nearby the trial medication. A complete randomization list will be delivered upon request by the pharmacy after data is fixed in the data analysis phase.

6.5 Blinding

The trial medication will be masked by the pharmacy. The Pharmacy of the Capital Region of Denmark will provide the part of the interventional medicine composed of tablets (ibuprofen or matching placebo). The original tablets will be encapsulated with an opaque capsule. Patients, the ones administrating the intervention, other caregivers, outcomes assessors, data managers, statisticians, decision makers, and writers of the manuscript will all be blinded to the intervention.

Statistical analyses will be performed with the two intervention groups coded as 'A', and 'B', by two independent blinded statisticians. Two blinded conclusions will be drawn by the Steering Committee assuming that either 'A', or 'B' is the placebo group. Based on the blinded conclusions, an abstracts agreed upon by the steering committee will be written and published along with the main publication.

The trial medicine will be packed and labelled by the pharmacy in accordance with the Good Manufacturing Practice (GMP) regulations. Each patients receives medication as stated under section 6 “Trial interventions”. The sponsor has a set of sealed, opaque envelopes with the patients’ allocation. The list of allocation numbers will only be revealed for the investigators when the data has been analysed and abstracts and conclusion covering the different possibilities for interpreting the trial results have been agreed upon by the steering committee.

7 Outcomes

7.1 Primary outcome

- A composite outcome of either death, acute myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, renal failure, major bleeding, re-operation, gastrointestinal ulcer, or readmission within 90 days postoperatively.

7.2 Secondary outcomes

- Hospital free days within 90 days postoperatively.
- A composite outcome of ibuprofen related adverse events based on eight-day postoperative diary: pain or discomfort from the epigastrium, reflux, diarrhoea.
- A composite outcome of opioid related adverse events based on eight-day postoperative diary: nausea, vomiting, constipation, sedation, headache, mood changes, mouth dryness.
- Health related quality of life questionnaire via EQ-5D-5L after 90 days and one year postoperatively.

The definition of ibuprofen related adverse events and opioid related adverse events are based on a selection of the most frequent (>10%) adverse events according to the product summary of "Ibumetin" (Appendix 3) and "Morfin 'DAK'".[69] The adverse events are patient reported. Further definition is elaborated in Appendix 4.

7.3 Explorative outcomes

- Proportion of individual serious adverse events in the composite primary outcome
- Proportion of individual adverse events of ibuprofen and opioid in the composite secondary outcome.
- Postoperative pain levels, analgesic treatment, opioid consumption, based on an eight-day postoperative diary and a questionnaire 14 days after surgery.

7.4 Definition of outcomes

Renal failure will be defined according to the RIFLE criteria.[83] Renal failure is defined according to RIFLE criteria, as "Failure of kidney function", "Loss of kidney function", and "End-stage of kidney disease".

	Changes in s-creatinine	**Changes in GFR**	**Urine output**
Risk of kidney dysfunction	Increase >50%	Decrease >25%	<0.5 ml/kg/hour for >6 hours
Injury to the kidney	Twofold increase	Decrease >50%	<0.5 ml/kg/hour for >12 hours
Failure of kidney function	Threefold increase or ≥ 350 µmol/L with an acute rise of ≥44 µmol/L	Decrease >75%	<0.5 ml/kg/hour for >24 hours or anuria for >12 hours
Loss of kidney function	Loss of kidney function, which requires dialysis, lasting longer than 4 weeks		
End-stage kidney disease	Loss of kidney function, which requires dialysis, lasting longer than 3 months		

Major bleeding will be defined as fatal bleeding, and/or symptomatic bleeding in critical area or organ, and/or bleeding causing fall in haemoglobin level of 1.24 mmol/l, or leading to transfusion to two or more units of whole blood or reed cells.[84,85]

Gastrointestinal ulcer will be defined as mucosal damage of the ventricle, lower oesophagus, duodenum or jejunum diagnosed by esophagogastroduodenoscopy procedure. Additional symptoms hereof: anaemia, hematemesis, melena, or heme-positive stool suggesting bleeding.

Further definitions and data sources are elaborated in Appendix 4.

7.5 Data collection

Table 2: overview of data collection

Data	Data source	Time
Date of birth, height, weight, ASA-score, medical history, type of surgery, type of anaesthesia, length of stay	Electronic medical record. 'Landspatientregisteret'. Patient reported.	Before intervention period and after the follow-up period (register data).
Medication (analgesic used prior to participating in the trial, use of diuretics, ACE-inhibitors, or angiotensin II antagonists prior to participating in the trial)	Electronic medical record. 'Lægemiddelstatistikregisteret'. Patient reported.	Before intervention period and after the follow-up period (register data).
Trial medication	Patient reported.	During intervention period.
Composite outcome of serious adverse events	Electronic medical record. 'CPR - Det Centrale Personregister'. 'Landspatientregisteret'. Patient reported.	After the end of follow-up period and one-year after.
Hospital free days	Electronic medical record. 'Landspatientregisteret'.	After the end of follow-up period.
Adverse events of ibuprofen and opioids	Patient reported in eight-day diary.	During intervention period.
Health related quality of life (EQ-5D-5L questionnaire)	Patient reported.	After the end of follow-up period.
Pain, analgesic treatment, opioid consumption	Patient reported in eight-day diary and reported in a questionnaire 14 days postoperatively. 'Lægemiddelstatistikregisteret'.	During intervention period and after the end of follow-up period.

Data collected from different sources will be compared by to independent investigators in case of discrepancy.

In case of data collected from a paper diary, the completed diary will be sent to the Central Unit at Zealand University Hospital and Næstved Hospital and registered in the eCRF by the investigators at the Central Unit. Please view section 7.6 "Follow-up".

7.6 Method and timing

Table 3: timeframe for individual participants

Study periods	**Screening, inclusion, and randomization**		**Intervention**	**Questionnaire**	**Follow-up – end of trial**	**Planned substudies**
	-2 months to -1 day	*Day 0*	*0-7 days*	*14 days*	*90 days*	*1 year*
Orthopaedic and pre-anaesthesia consultation	X					
Oral and written informed consent	X	X				
hCG test*		X				
Admission on the day of surgery		X				
Randomization		X				
Intervention			X			
Primary outcome						
Composite outcomes of serious adverse events					X	X
Secondary outcomes						
Hospital free days					X	
Adverse events of ibuprofen and opioids			X			
Health-related quality of life (EQ-5D-5L)					X	
Explorative outcomes						
Proportion of individual serious adverse events of the primary outcome					X	
Proportion of individual adverse events of ibuprofen and opioids			X			

Pain, analgesic treatment and opioid consumption			X	X		
Substudies						
Composite outcome of serious adverse events						X
Co-factors as predictors of persistent pain and opioid consumption					X	X
Preoperative diuretics, ACE-inhibitors/AT-II-antagonists effect on risk of renal failure					X	

*The hCG pregnancy test will be obtained on the day of surgery before randomization. The test is a urine-hCG test. All women in the fertile age will be tested. Postmenopausal state is defined as no menstruation for 12 months without alternative medical cause.

Primary outcome

The primary outcome will be assessed by a blinded adjudication committee. The proportion of incidence will be recorded from postoperative day 0 to day 90. The number of incidences will be recorded via the electronic medical record and retrieved from the Civil Registration System Registry: “CPR - Det Centrale Personregister", and the Danish National Patient Registry “Landspatientregisteret” 90 days postoperatively. Additional, by contacting the patients 90 days postoperatively. The definition of the components is elaborated in Appendix 4, including data sources.

The blinded adjudication committee will consist of two independent investigators who each will estimate components of the composite outcome in the eCRF from the Central Unit.

Further, a substudy will conduct incidence of composite of serious adverse events one year postoperatively.

Secondary outcomes

Hospital free days

Number of hospital free days will be recorded by the electronic medical record systems, by the Civil Registration System “CPR - Det Centrale Personregister” and by the Danish National Patient Registry - “Landspatientregistret” - after 90 days postoperatively.

Adverse events of ibuprofen and opioids
Distribution of incidence will be recorded from postoperative day 1 to day 8 via an eight-day electronic or paper diary questionnaire. The classification is elaborated above in section 7.2 "Secondary outcomes". The definition of the components is elaborated in Appendix 4.

Health related quality of life questionnaire
The EQ-5D-5L questionnaire will be retrieved electronically via Redcap 90 days postoperatively. The patients will be reminded of the questionnaire during the phone call, mail, or e-Boks mediated contact at 90-days postoperatively.

Explorative outcomes

Proportion of individual serious adverse events
The proportion of individual serious adverse events according to the primary outcome, will be recorded from postoperative day 0 to 90. The number of incidences will be recorded via the electronic medical record and retrieved from the Civil Registration System Registry "CPR - Det Centrale Personregister", and the Danish National Patient Registry "Landspatientregisteret" 90 days postoperatively. Additionally, by contacting the patients 90 days postoperatively.

Proportion of individual adverse events
The proportion of individual adverse events of ibuprofen and opioids will be recorded from the eight-day electronic or paper diary questionnaire from postoperative day 1 to day 8.

Pain levels and analgesic treatment
Pain levels and need of further analgesic treatment, including opioid consumption will be recorded from the eight-day electronic or paper diary questionnaire from postoperative day 1 to day 8. Further, it will be recorded via an electronic questionnaire 14 days postoperatively.

A substudy of persistent pain and opioid consumption at 90 days and one year after surgery will be conducted. Please view the section below for further details.

Follow-up

Data will be collected from the electronic medical record and retrieved from the Civil Registration System "CPR - Det Centrale Personregister" and the Danish National Patient Registry "Landspatientregisteret". Patient will be contacted at postoperative day 14 and day 90 via phone, mail or e-Boks. Data collection schedule is stated under 7.5 "Data collection". Follow-up will primarily be performed by local investigators at the Central Unit at Zealand University Hospital Køge and Næstved Hospital. Access to cross-regional medical record systems will be obtained prior to conduction of the trial.

7.7 Planned substudies

One-year follow-up for the composite outcome of serious adverse events conducted by registers, the electronic medical record and by contacting the participants via phone, mail or e-Boks.

Furthermore, we plan to investigate the effect of different co-factors, incl. preoperative analgesic treatment, type of anaesthesia, gender, age, good health, and type of surgery, as predictors of persistent pain and opioid consumption at 90-days, and one-year after surgery. Data of opioid consumption will be retrieved from 'Lægemiddelstatistikregisteret' at 90 days and one year after surgery.

We plan to investigate the coherence of preoperative use of diuretics, ACE-inhibitors or Angiotensin-II-antagonists and postoperative risk of renal failure (triple whammy).

Additional, a bayesians re-analysis of the primary and secondary outcomes up to 90 days postoperatively. A protocol will be published for further details.

7.8 Patient involvement

We collaborated with six patients that were planned for future arthroplasties. These patients prioritized the primary composite outcome, beginning with the most patient important one (Appendix 5). Further, six patients (three planned for hip arthroplasties and three planned for knee arthroplasties) reviewed the patient information on participating of the trial, the eight-day diary and the questionnaire given at postoperative day 14. Additional, we will collaborate with patients regarding dissemination of the results of the trial. Further patient involvement may follow where relevant.

8 Ethical considerations

Ibuprofen is well-known and registered drug for pain alleviation. Ibuprofen is the most frequently used NSAID and is widely included and recommended as a part of basic analgesic treatment in the perioperative setting. [25,29,41,43] Ibuprofen is available 'over-the-counter' in doses of 200-400 mg per tablet. [41,79] As monotherapy, ibuprofen has shown a morphine-sparing effect. [31,70] Safety data is well established in the non-surgical population, including in cardiac patients. [42,49,61,74,78] However, safety data are short in supply after hip and knee arthroplasties. [43] This is problematic, as patients hereby are not able to give a full informed consent to such treatment. Further, it is a daily concern for doctors responsible for the analgesic treatment.

We believe that participating in this trial is not associated with increased risks compared to current clinical treatment.

In this trial, treatment duration is relative short (eight-day period) and reflect already instituted treatment at Danish Departments of Orthopaedics by a recent national survey (own data, not published yet).

Ibuprofen is approved by the European Medicines Agency and is recommended for postoperative pain treatment after elective hip and knee arthroplasties.[29,79] Additionally, ibuprofen is available 'over-the-counter'.[34,41,79] Therefore, this trial will not apply increased risk in the participating patients as the trial reflects the clinical reality and standard postoperative pain treatment.

Overall, previous studies on safety of postoperative NSAID treatment after major orthopaedic surgeries are retrospective or prospective cohort studies which are inconsistent of safety with ibuprofen.[80] This randomized clinical trial will makes us able to determine the safety of short-time postoperative treatment with ibuprofen.

Informed consent

The trial will be conducted according to national and international standards of good clinical practice (GCP). This protocol and any amendments will be submitted to the ethical committee for review and formal approval before conducting the trial. All patients considered for the trial through the medical record will be provided with written and verbal information about the trial so the patients' can make an informed decision about their participation in the trial. The written information and the consent form will be subjected to review and approval by the ethical committee.[86] This consent form must be signed by the participants and by the local investigator.

All patients scheduled for hip and knee arthroplasties at the Department of Orthopaedics at Næstved Hospital, Zealand University Hospital, Bispebjerg Hospital, Gentofte Hospital, Nordsjællands Hospital Hillerød, Odense University Hospital including Svendborg Sygehus, Vejle Hospital, Silkeborg Regional Hospital, Aalborg University Hospital Farsø, and Gildhøj Private Hospital will be invited to take part in the trial. More sites will be enquired to participate in the trial.

Investigator and local investigators will obtain some information from the patients' medical record regarding inclusion and exclusion criteria in advance of the patient consent during the pre-screening (view section 4.3). The information from the medical record prior to obtaining informed consent according to section 4.3 is according to the Danish Health Care Act § 46, subsection 1 with the right to transmission given by the treatment responsible physician.

The first contact to the patient will take place at either the ambulatory visit by the surgeon, at the pre-anaesthesia consultation by the anaesthesiologist or at the patient seminar at the Orthopaedic Department by the investigator. If such a seminar is replaced with a phone call by the department's nurses, the patients will be asked if they consent to be contacted by the research team via telephone, documented in the medical record.

Depending on local circumstances, the patients will be verbally informed of the trial at the orthopaedic ambulatory, at the pre-anaesthesia consultation or at the patient seminar. When informing the patients about the trial, the patients will be handed out the participant information.

If this is not the case, written information is handed out to the patient by the clinicians and the patient gives consent to be contacted by the research team via telephone, documented in the medical record.

If information is provided over the phone, patients will receive the written information electronically or by mail to their home address prior to written consent before surgery. However, the patients will be informed of the right to receive the information in paper format when admitted to the department.

The second contact will depend on local clinical practice, and may be either at the pre-anaesthesia consultation, at the seminar, by telephone by the investigator, or at time of admission prior surgery.

The verbal information will be given by one of the investigators, or by a qualified local doctor trained in obtaining the informed consent.

If information is given by telephone, the patient will be informed of a physical meeting with the local investigator prior to informed written consent. This will be at the latest, the day of surgery.

At the beginning of the consultation, before oral information regarding the trial is given, the patient will be informed that they have the possibility of having a companion present. The interview will be conducted in a closed room without distractions or interruptions. The patient will be given relevant and necessary time (a minimum of 24 hours) to consider the request. Consent shall, at the latest, be obtained on the day of surgery before postoperative analgesic treatment is given.

Written informed consent will be obtained by a doctor. The doctor will be qualified and will have the knowledge and information regarding the trial to answer potential questions from the

patients. The informed consent will be signed by the patient and the doctor obtaining the informed consent before inclusion in the trial and before intervention.

Prior to obtaining the informed consent, project staff (project nurse or project scholar (medical student)) may pre-inform the patients regarding the trial.

The patients will be informed that:

- Participation is voluntary and withdrawing from the trial is possible at any time.
- What treatment they will receive if they choose not to participate or wish to withdraw from the trial.
- Randomization will take place on the day of surgery.
- Information such as age, height, weight, medical history, analgesic used prior to participating in the trial, diuretic use and use of ACE-inhibitors and angiotensin-II-antagonist prior to participating in the trial, type of surgery and type of anaesthesia will be obtained from their medical record. This is to describe the different intervention groups.
- All information obtained during the trial will be treated with strict confidentiality and will be anonymized when the trial is finished. The Danish Data Protection Agency and The Danish Medicines Agency will supervise the project.
- With regard to national law, The Danish Medicines Agency, alongside sponsor, investigator, and the GCP-unit, will have access to the patient's medical record to perform control and inspection of the project.
- Collection of the eight-day patient dairy, follow-up 14 and 90 days postoperatively, and one-year after surgery will be conducted by a central unit of investigators located at Zealand University Hospital Køge and Næstved Hospital.
- All parties above are bound to secrecy, and that the trial will be performed in compliance with the General Data protection Regulation and Data Protection Act.

A copy of the information and consent declaration will be given to the patients.

9 Assessment of safety

9.1 Safety variables and definitions

Adverse events

Adverse events are defined as any toward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. It can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of medicinal product, whether or not considered related to the medicinal product.

Adverse reactions

Adverse reactions are defined as any unintended responses to a medicinal product related to any dose administrated, which have a causal relationship with this treatment.

Serious adverse events or serious adverse reactions

Serious adverse events and serious adverse reactions are defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (in the investigators opinion, the patient was in immediate risk of death from the adverse event when it appeared).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.[87]

Suspected unexpected serious adverse reactions (SUSARs)

A SUSAR is defined as any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with the applicable product information available to date).
A summary of product characteristics for ibuprofen (Appendix 3) will be used as a reference document when it is assessed whether a serious related adverse reaction is expected or unexpected.

Adverse events, adverse reactions, serious adverse events, serious adverse reactions and SUSARs will be recorded and analysed.

9.2 Method and timing

Adverse events, adverse reactions, serious adverse events, serious adverse reactions and SUSARs will be recorded during the trial period from postoperative day 0 to 90.

Adverse events and adverse reactions will be patient reported and collected during the eight-day diary from postoperative day 1-8. Serious adverse events, serious adverse reactions and SUSARs will be recorded from postoperative day 0-90 via the electronic medical record, registers and by contacting the patients at 90 day postoperatively.

9.3 Adverse events reporting and follow up

Reporting

The local investigator and investigators at the Central Unit are responsible for ensuring that all adverse events are recorded in the electronic CRF. During admission, the local investigator will ensure this. During follow-up, the investigators at the Central Unit will ensure this on the behalf of the sponsor.

The following rules apply for reporting to the authorities:

Patients with adverse events will be monitored with appropriate clinical assessment and laboratory test according to the decision of the attending doctor. All adverse events will be followed until satisfactory recovery and stabilization.

Serious adverse reactions and serious adverse events will be reported immediately by the investigator to the sponsor, within 24 hours from being informed of these. The serious adverse reactions will be reported by the sponsor annually to the Danish Medicines Agency and the Research Ethics Committee, including a report on the safety of trial patients.

SUSARs will be immediately reported by the sponsor to the Danish Medicines Agency and the Research Ethic Committee as stated in the Regulation (EU) No 536/2014. Before reporting a SUSAR to the Agency by the sponsor, an emergency unblinding must occur for the individual patient before reporting.

Fatal or life-threatening SUSARs will be reported within seven days of the sponsor becoming aware of them, and within eight days of the report the sponsor will inform the Danish Medicines Agency of all relevant information on the follow-up. All other SUSARs will be reported to the same authorities within 15 days of the sponsor being informed of these.

All reports will be accompanied by comments on any consequences influencing the trial.

At the end of the trial, the final report shall contain a description of all adverse events.

The sponsor is responsible for ongoing monitoring of the trial's risk and benefit relation. The sponsor will keep oversight of the trial. The primary investigator will keep oversight of the local site. If there arise or are seen to be situations that may affect the safety of the trial participants or the performance of the trial, these must always be immediately reported to the Danish Medicines Agency. Similarly, reports should also be made to all investigators and Research Ethics Committees involved.

Severity of adverse event

If present, an adverse event will be graded according to the following scale:

- 1 = slight.
- 2 = moderate.
- 3 = severe.
- 4 = life-threatening.

Relationship of adverse event to clinical trial intervention product

The medical investigator should attempt to identify all clinical and objective reactions from patients in the treatment and determine their relationship with the trial medication. This will be graded:

- Not related: no temporal relationship, other aetiologies are very likely the cause.
- Possibly related: less clear correlation, other aetiologies are also possible.
- Probably related: clear temporal correlation with improvement on discontinuation of medication, and not reasonably explained by the patient's known clinical condition.
- Related: clear temporal relationship with repeated treatment test or clinical assessment.
- Unknown: causality is not assessable, e.g., due to insufficient evidence, conflicting data, or poor documentation.

Recording of adverse events

Adverse events in study period must be recorded in the patient's eCRF if mentioned by the patients.

The following variables must be recorded:

- Description of event.
- Onset and end of event.
- Severity.
- Relation to intervention product.
- Action taken.
- Outcomes.

The severity of the adverse events and the relationship with the trial medication must be assessed in accordance with the guideline described.

Adverse events, adverse reactions, serious adverse reactions, serious adverse events, and SUSARs will be recorded during the intervention period when patients are admitted and at the end of the follow-up period, both 90 days after surgery and at the one-year follow-up.

Type and duration of the follow up of participants after adverse events

Patients with adverse events will be monitored with appropriate clinical assessment and laboratory tests according to the decision of the attending medical doctor. All adverse events will be followed until satisfactory recovery or stabilization.

10 Statistical plan and data analysis

10.1 Sample size estimation

The sample size calculation of the primary outcome is based on data from a large Danish cohort study[15] with 36,935 total hip and knee arthroplasty procedures, a large Danish register study[12] of 7449 patients with mixed surgical procedures, and from a large randomized clinical trial[31] (the PANSAID trial) of 556 patients undergoing total hip arthroplasty surgery with ibuprofen as postoperative analgesic treatment. The Danish cohort study[15] found a risk readmission of 7.7% within 90 days postoperatively. The Danish register study[12] found the risk of events in a composite outcome with six items (death, myocardial infarction, pulmonary embolism, cerebral thrombosis or cerebral haemorrhage, gastrointestinal haemorrhage, dialysis, or reoperation) of 2.35% at 90 days after elective orthopaedic surgery, and the PANSAID trial[31] found a risk of serious adverse events in the ibuprofen group of 15% and in the paracetamol group of 11%.

With a composite outcome of 10 items, including readmission rate of 7.7%, it is therefore reasonable to expect a proportion of serious adverse events according to the composite outcome, of 8% in the ibuprofen group.

Accepting a risk of type II error of 20%, a risk of type I error of 5%, with a power of 80%, and a proportion of serious adverse events according in the composite outcome in the ibuprofen group of 8%, we will need 2902 (2x 1451) patients to detect or discard an effect corresponding to a relative risk reduction of 33% in the control group. We expect the proportion of missing data to be minimal according to previous randomized trials with total hip and knee alloplastic patients.[31,88]

Due to block size of 4, 6 and 8, delivered in chunks of 24, the total number of patients will be 2904.

10.2 Statistical methods

The trial will be completed when 2904 patients are included in the trial. Statistical analyses will be performed by two independent statisticians.

The primary analysis will be an intention to treat analysis, where all randomized patients undergoing hip and knee arthroplasties will be included in the statistical analysis and analysed according to the group to which they were originally assigned. All analyses will be adjusted for site only. Dichotomous outcomes will be analysed using logistic regression, continuous outcomes will be analysed using linear regression, and count data outcomes will be analysed using van Elteren test. We will additionally perform an exploratory analysis on the primary outcome using win-ratio. [89] All outcomes will be adjusted for site.

Test of interaction will be performed of the primary and secondary outcome regarding type of surgery (primary or secondary procedure, hemiarthroplasty or total arthroplasty), age, gender, preoperative use of NSAIDs. Further elaboration will be made in the statistical plan.

Per protocol analyses will be analysed excluding patients with major protocol violations. Major protocol violations are defined below.

Major protocol violations will be defined as:

- Patients that did not get any randomized allocated trial treatment, *or*
- Patients that did not get surgery, *or*
- Patients withdrawn from the trial intervention, not allowing the use of registered data

Missing data and assessments of underlying statistical assumptions will be handled according to the recommendation by Jakobsen et al. [90]

10.3 Significance

We only assess one primary outcome and consider all remaining analyses as hypothesis generating or support the primary outcome result. Hence, the overall type I error of 5% is chosen. The power of this trial is 80%, beta = 20%.

Results will be described with frequencies (percentage). Distributions and differences between groups will be described with 95% CI. Mean values and standard deviation, as well as median and inter-quartile values as appropriate.

10.4 Interim analysis

A Data Monitoring and Safety Committee (DMSC) will be established and will perform the interim-analysis after 90-day follow-up period of 2x 700 patients (Appendix 6). The DMSC will receive data to analyse the primary outcome but can request additional data if deemed needed. The DMSC will use LanDeMets group sequential monitoring boundaries based on O'Brien Flemming alfa-spending function to decide if the trial should be stopped early.[91] The DMSC will then inform the primary investigator if the trial should continue or be stopped early. If the trial continuous it is the DMSC's decision if (or when) an additional interim analysis should be conducted. The DMSC will receive blinded data but can request to receive unblinded data at any time point.

11 Direct access to source data/documentation

The trial will be conducted in accordance with the applicable rules on clinical trials involving people in respect of quality control and quality management and will follow the GCP guidelines.

The principal investigator and co-investigators at the hospital are responsible for managing and archiving data in accordance with current regulations.

Data collected in the form of a worksheet and records will only be made available to third parties in accordance with Danish law, which means in connection with monitoring by the GCP units, as well as upon inspection by authorized representatives of relevant authorities.

12 Data handling and record keeping

12.1 Protection of participant data

All information will be treated confidentially and the persons responsible for this trial are bound to confidentiality. When reporting the test results, patients will be anonymized.

The principal investigator will create an identification list of all patients who have been given trial numbers. This list will contain the full names and CPR numbers.

The trial will be notified to the Danish Protection Agency.

The investigators will ensure that the projects follow the rules of GCP.

Data collected in the form of a worksheet and records will only be made available to third parties in accordance with the act on processing of personal data, which means in connection with monitoring by GCP units, as or upon inspection, by authorized representatives of relevant authorities.

Patients will be informed about the following in writing:

- Results will be stored and analysed in a computer.
- All information will be treated confidentially.
- Patients will be anonymized in reporting of the results of the trial.
- The possibility of a review by public authorities in the event that they require access to relevant information.
- GCP units will have to access to trial information.
- The study will be performed in compliance with the general Data Protection Regulation and the Data Protection Act.
- Patients have the right to request from the controller access to and rectification or erasure of personal data or restriction of processing concerning the data subject or to object to processing.
- Patients have the right to lodge a complaint with a supervisory authority.

12.2 Case Report Form

An eCRF will be completed for each participant included in the trial. Only the investigators or their deputy will enter data in the eCRF, including investigators at the Central Unit. The eCRF will be in a database which is hosted and maintained by Redcap (https://redcap.regionsjaelland.dk/). Every alteration, corrections or typing will be traceable through a full log of all activities (the incorrect or altered information will remain visible and legible). Data will be stored in twenty-five years after finishing the trial. Afterwards all paper material will be maculated, and electronic data will be completely anonymized.

Source data is defined in section 7.5 ”Data collection” and in appendix 4.

The Central Unit will enter data in the eCRF during follow-up, and in case of paper diary during the intervention period.

12.3 Data from the electronic medical record

Patients scheduled to elective hip or knee arthroplasties will be screened for inclusion. Screening will obtain data from the electronic medical record prior to consent from the patients. Screening data will be entered in the eCRF. Data collected prior to consent will contain information regarding type of surgery, side for surgery, and medical history. This is to review whether the patient fulfils the trials inclusion- and exclusion criteria. If the patient is not included in the trial, data of inclusion- and exclusion criteria including reason for not participating in the trial will be collected (e.g. fulfils exclusions criteria, do not wish to participate etc.).

Information regarding screening will be used for the rate of inclusion and be part of a flow-chart of inclusion of participants.

Data recorded from the electronic medical record after informed consent are elaborated in section 7.5 “Data Collection”. Data of patient demographics will be used for describing patient characterises and used for stratification as part of sensitivity analysis.

13 Quality control and quality assurance

The trial will be monitored according to Danish law and ICH-GCP-guidelines [82] by Copenhagen University Hospital's, Odense University Hospital's and by Aalborg/Aarhus University Hospitals' GCP Units.

The investigators will see to that all staff involved in the trial will be adequately trained for their role. A log of who is trained (dates and signatures) will be kept.

14 Trial organization

14.1 Steering committee

- Christina Cleveland Westerdahl Laursen (Zealand University Hospital)
- Joakim Steiness (Zealand University Hospital)
- Kasper Gasbjerg (Zealand University Hospital)
- Kasper Thybo (Næstved-Slagelse-Ringsted Hospitals)
- Anne Sofie Nautrup Therkelsen (Zealand University Hospital)
- Troels Haxholdt Lunn (Bispebjerg Hospital)
- Søren Overgaard (Bispebjerg Hospital)
- Daniel Hägi-Pedersen (Næstved-Slagelse-Ringsted Hospitals)
- Mohammad Samir Munir (Næstved-Slagelse-Ringsted Hospitals)
- Claus Varnum (Vejle Hospital)
- Ben Kristian Graungaard (Herlev-Gentofte Hospital)
- Thomas Bjerno (Herlev-Gentofte Hospital)
- Martin Lindberg-Larsen (Odense University Hospital)
- Niels Anker Pedersen (Gildhøj Hospital)
- Kai Henrik Wiborg Lange (Nordsjællands Hospital, Hillerød)
- Müjgan Yilmaz (Nordsjællands Hospital, Hillerød)
- Andreas Kappel (Aalborg University Hospital)
- Thomas Jakobsen (Aalborg University Hospital)
- Charlotte Runge (Silkeborg Regional Hospital)
- Jacob Beck (Silkeborg Regional Hospital)
- Stig Brorson (Zealand University Hospital)
- Janus Christian Jakobsen (Copenhagen Trial Unit)
- Ole Mathiesen (Zealand University Hospital)

Additional members may be added as more sites will participate.

14.2 Primary investigators

- Christina Cleveland Westerdahl Laursen (Zealand University Hospital)
- Troels Haxholdt Lunn (Bispebjerg Hospital)
- Mohammad Samir Munir (Næstved-Slagelse-Ringsted Hospitals)
- Claus Varnum (Vejle Hospital)
- Ben Kristian Graungaard (Herlev-Gentofte Hospital)
- Martin Lindberg-Larsen (Odense University Hospital, incl. Svendborg Hospital)
- Niels Anker Pedersen (Gildhøj Hospital)
- Kai Henrik Wiborg Lange (Nordsjællands Hospital, Hillerød)
- Andreas Kappel (Aalborg University Hospital)
- Jacob Beck (Silkeborg Regional Hospital)

Additional primary investigators may be added as more sites will participate.

14.3 Roles in the trial

- Christina Cleveland Westerdahl Laursen: coordinating primary investigator, 1st author.
- Troels Haxholdt Lunn: initiator, primary investigator, co-supervisor for CCWL, 2nd author.
- Daniel Hägi-Pedersen: initiator, sponsor, co-supervisor for CCWL, 3th author.
- Janus Christian Jakobsen: initiator, investigator, chief methodologist, statistician, co-supervisor for CCWL, penultimate author.
- Ole Mathiesen: initiator, investigator, primary supervisor for CCWL, last author.
- GCP-units: monitor.
- Pharmacy: blinding, labelling, packing of trial medication.
- Copenhagen Trial Unit: randomization

15 Legal aspect

15.1 Finance and insurance

The trial is initiated by professor, PhD Ole Mathiesen (Zealand University Hospital); associate professor, DMsc, PhD Troels Haxholdt Lunn (Bispebjerg Hospital); Head of research, Associate professor, PhD Daniel Hägi-Pedersen (Næstved-Slagelse-Ringsted Hospital); and professor, PhD Janus Christian Jakobsen. All investigators have substantial experience in conducting multicentre trials. The PERISAFE trial steering committee will include members from each of the participation departments and will supervise and coordinate the trial.

The trial cost includes payment of trial personal, trial medication, miscellaneous registration fees, monitoring etc. There is no payment of participants for participation in the trial. The financial support provided is a fixed amount to cover the trial cost. The costs are met by Department of Anaesthesiology, Zealand University Hospital Køge, Department of Anaesthesiology at Næstved-Slagelse-Ringsted Hospital, Department of Anaesthesiology at Bispebjerg Hospital, and by external funding. We have currently received a funding of 5,000,000 DKR from Sygeforsikring "danmark", 2,060,000 DKR from Independent Research Fund Denmark, 500,000 DKR from the Zealand Region, 250,000 DKR from Lægeforeningens Forskningsfond, 300,000 DKR from Skibsreder Per Henriksen, R. og Hustrus fond, and a donation from Independent Research Fund Denmark (awaiting final confirmation on amount donated). This makes it possible to start the project. Funding will be disbursed to the Anaesthesiological Research Centre of the Department of Anaesthesiology at Zealand University Hospital, Køge. Further funding will be applied for.

The salary for Christina Cleveland Westerdahl Laursen is ensured by Zealand University Hospital Køge, and from external funding.

The investigators have no financial interest in the trial.

The trial takes place at the Department of Orthopaedics at Næstved Hospital, Zealand University Hospital, Bispebjerg Hospital, Gentofte Hospital, Nordsjællands Hospital Hillerød, Odense University Hospital including Svendborg Sygehus, Vejle Hospital, Silkeborg Regional Hospital, Aalborg University Hospital Farsø, and Gildhøj Private Hospital.

We except further hospitals to participate in the trial. The trial will be covered by the Danish act on Right to Complain and Receive Compensation within the Health Service.

15.2 Publication plan

A protocol article and detailed analysis plan based on the present protocol will be published in fall 2023. On basis of the data, the investigator will write a report of the trial. This report will be forwarded to the relevant authorities. All results (negative, positive, or inconclusive) will be published. A full anonymized dataset will be made available by request at 9 months after last patient's last visit. The report will also form the basis of the manuscript to be submitted for publication with the following authors:

1. Christina C.W. Laursen
2. Troels H. Lunn

3. Daniel Hägi-Pedersen
4. Anne Sofie Nautrup Therkelsen
5. Claus Varnum
6. Kai H.W. Lange
7. Müjgan Yilmaz
8. Niels A. Pedersen
9. Andreas Kappel
10. Thomas Jakobsen
11. Mohammad S. Munir
12. Ben K. Graungaard
13. Thomas Bjerno
14. Charlotte Runge
15. Jacob Beck
16. …
17. …
18. Stig Brorson
19. Martin Lindberg-Larsen
20. Søren Overgaard
21. Janus C. Jakobsen
22. Ole Mathiesen

Order may change, but CCWL will always be the first, THL the second, DHAG the third, JCJ the penultimate and OM the last author. We plan to include authorships on senior investigators from the departments of Anaesthesiology and Orthopaedic Surgery from each participation site, if relevant. Additional co-authorships may be granted according to number of included patients (one additional for each 50 patient) and according to the guidelines from the International Committee of Medical Journal Editors (ICMJE).[92] Co-authorships will be decided by the steering committee. Order of authorships may follow numbers of included patients.

Funding sources will have no influence on the interpretation of data.

Explorative outcomes will be published as independent articles where appropriate.

15.3 Intellectual property rights

Data belongs to the coordinating investigator (CCWL), and Professor Ole Mathiesen, Centre of Anaesthesiological Research, ZUH. The investigators and co-investigators at the hospitals are responsible for managing and archiving data in accordance with current regulations. Data will be published anonymized according to ICMJEs guidelines.[92]

16 Appendix

Appendix 1: existing reviews and meta-analysis on perioperative NSAID usage in orthopaedic patients

Appendix 2: overview of randomized clinical trials of NSAIDS in orthopaedic total hip and knee arthroplasty surgeries

Appendix 3: summary of product characteristics of ibuprofen in original language

Appendix 4: definition of components of the primary, secondary and explorative outcomes measurements

Appendix 5: patient ranged outcomes

Appendix 6: charter for the independent Data Monitoring and Safety Committee (DMSC) of the PERISAFE trial

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Appendix 1

Table 1: existing reviews and meta-analysis on perioperative NSAID usage in orthopaedic patients

Author, year	Type of surgery	Type of NSAID	Included studies	Quality assessment	Meta-analysis of adverse events	Trial Sequential analysis	GRADE	Primary focus	Main conclusion
Geng, 2022[1]	Orthopaedic	Celecoxib	RCTs*	RoB**	Yes	No	No	Efficacy	Celecoxib is not related to more adverse events after total knee arthroplasty
Al Farii, 2021[2]	Orthopaedic	Mixed NSAIDs	RCTs*	Publication bias	Yes	No	No	Safety	NSAIDs used in less than two weeks does not affect bone healing, when used for more than 4 weeks it does effect bone healing.
Fillingham, 2020[3]	Orthopaedic	Mixed NSAIDs	RCTs*	RoB**	Yes	No	Yes	Efficacy	NSAIDs are not associated with increased adverse events
Constantinescu, 2019[4]	Orthopaedic	Mixed NSAIDs	RCTs* and observational	RoB** and RoBINS-I	Yes	No	No	Safety	NSAIDs is not related to impaired soft tissue healing, though celecoxib may inhibit tendon-to-bone healing
Wan, 2019[5]	Orthopaedic	Celecoxib	RCTs*	Jadad	Yes	No	No	Efficacy	Celecoxib does not increase adverse events following arthroscopy
Wheatley, 2019[6]	Orthopaedic	Mixed NSAIDs	RCTs* and observational	Newcastle-Ottawa and Jadad	Yes	No	No	Safety	Indication of negative effect of NSAIDs on bone healing
Borgeat, 2018[7]	Orthopaedic	Mixed NSAIDs	RCTs* and observational	Jadad and RoB**	No	No	No	Safety	NSAIDs does not have a proven negative effect on bone healing
Du, 2018[8]	Orthopaedic	Parecoxib	RCTs*	RoB**	Yes	No	No	Efficacy	Parecoxib is not related to more adverse events after total knee arthroplasty

Marquez-Lara, 2016[9]	Orthopaedic	Mixed NSAIDs	RCTs* and reviews	Coleman	No	No	No	Safety	NSAIDs does not have a proven negative effect on bone healing
Jirarattanaphochai, 2008[10]	Orthopaedic	Mixed NSAIDs	RCTs*	Modified Oxford Scale	Yes	No	No	Efficacy	NSAIDs does not influence the incidence of adverse events following lumbar spine surgery

* RCTs: Randomized Clinical Trials, ** RoB: Risk of Bias

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Appendix 2

Table 2: overview of randomized clinical trials of NSAIDS in orthopaedic total hip and knee arthroplasty surgeries.

Author, year	Title	Type of surgery	Total N	Primary outcome	Secondary outcomes	NSAID	Dose	Control	Interven-tion	Follow-up
Ready 1994[1]	Evaluation of intravenous ketorolac administered by bolus or infusion for treatment of postoperative pain	Orthopaedic (incl. total hip and knee arthroplasty), Gynaecology, General surgery	207	Morphine consumption 24h	Pain levels (VAS), adverse events patient evaluation	Ketorolac	30mg bolus and 5mg/h	Placebo	24h	24h
						Ketorolac	30mg bolus and 15mg/3h			
Etches 1995[2]	Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip and knee arthroplasty	Total hip and knee arthroplasty	174	Morphine consumption 24h, pain scores, adverse events		Ketorolac	30mg bolus and 5mg/h	Placebo	24h	24h
Alexander 2002[3]	Comparison of the morphine-sparing effects of diclofenac sodium and ketorolac tromethamine after major orthopedic surgery	Total hip and knee arthroplasty	102	Morphine consumption 24h	Pain score, PONV, sedation	Diclofenac	75mg bolus	Placebo	Bolus T0	24h
						Ketorolac	60mg bolus			
Hanna 2003[4]	Comparative study of analgesic efficacy and morphine-sparing effect of intramuscular dexketoprofen trometamol with ketoprofen or placebo	Total hip and knee arthroplasty	172	Total cumulative amount of morphine	Amount of morphine administered as a loading dose, time from the first dose of the study medication to the loading dose, time to first use of PCA.	Dexketo-profen	50mg/12h	Placebo	12h	24h

	after major orthopaedic surgery				Additional secondary variables were the scoring of pain intensity and quality of sleep.	Ketoprofen	100mg/12h			
Hubbard 2003[5]	Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia	Total knee arthroplasty	195	Cumulative morphine consumption	Proportion of patients requiring morphine between the time points; time to the first/last dose of morphine, patients' global evaluation of the study medication. Incidence of treatment-emergent adverse events, results from physical examinations, and changes in vital signs and clinical laboratory values	Parecoxib	20mg/12h	Placebo	36h	48h
						Parecoxib	40mg/12h			
Malan 2003[5]	Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty	Total hip arthroplasty	201	Morphine consumption 12h, 24h, 36h	Pain intensity, adverse events	Parecoxib	20mg/12h	Placebo	24h	36h
						Parecoxib	40mg/12h			

Inan 2007[6]	Efficacy of lornoxicam in postoperative analgesia after total knee replacement surgery	Total knee arthroplasty	46	Pain score	Morphine consumption, adverse events, Heart rate, blood pressure, respiratory rate	Lornoxicam	16mg bolus and 8mg/12h	Placebo	24h	48h
Martinez 2007[7]	The influence of timing of administration on the analgesic efficacy of parecoxib in orthopedic surgery	Total hip arthroplasty	62	Cumulative individual morphine consumption over the first 24 h after surgery.	Morphine titration in the PACU, morphine use, pain score in the PACU, time to first analgesic in the PACU, pain score, morphine- and parecoxib-related side effects during the follow-up period, and total RBC loss	Parecoxib	40mg/12h	Placebo	12h	24h
						Parecoxib	40mg/12h			
Meunier 2007[8]	Effects of celecoxib on blood loss, pain, and recovery of function after total knee replacement	Total knee arthroplasty	50	Radiostereo-metric analysis of prosthesis fixation	Consumption of analgesics, pain, range of knee motion (ROM), Subjective outcome via knee injury and osteoarthritis outcome score (KOOS)	Celecoxib	200 mg/12h	Placebo	3 weeks	1 year
Huang 2008[9]	Perioperative celecoxib administration for pain management after total knee arthroplasty – A randomized, controlled study	Total knee arthroplasty	80	VAS pain reduction	ROM, morphine-sparing effects, postoperative nausea, vomiting and blood loss	Celecoxib	200mg/12h	Placebo	5 days	7 days

Daniels 2013[10]	Analgesic efficacy and safety of a novel injectable formulation of diclofenac compared with intravenous ketorolac and placebo after orthopedic surgery - A multicenter, randomized, double-blinded, multiple-dose trial	Orthopaedic (incl. total hip and knee arthroplasty)	277	Sum of pain intensity differences over 5 intervals: 0 to 24, 0 to 48, 0 to 72, 0 to 96, and 0 to 120 h	Total pain relief over 0 to 24, 0 to 48, 0 to 72, 0 to 96, and 0 to 120 h. Proportion of patients attaining clinically reduction in pain intensity (30%). Pain intensity. Amount and frequency of rescue morphine administration. Patient global evaluation on a 5-point scale. Adverse events.	Diclofenac	18,5-37,5mg/6h	Placebo	1-5 days	5 days
						Ketorolac	15-30mg/6h			

Carmichael 2013[11]	An intensive perioperative regimen of pregabalin and celecoxib reduces pain and improves physical function scores six weeks after total hip arthroplasty:An intensive perioperative regimen of pregabalin and celecoxib reduces pain and improves physical function scores six weeks after total hip arthroplasty: A prospective randomized controlled trial	Total hip arthroplasty	47	Physical function assessed by 6 min walk test at six weeks following surgery.	Pain, physical function and psychosocial factors, adverse events	Celecoxib	100mg/12h	Placebo	5 weeks	6 weeks
Chelly 2013[12]	Safety of novel parentreral formulation of diclofenac after major orthopedic or Abdominal/Pelvic Surgery in a Population Including Anticoagulated, Elderly or Renally Insufficient Patients: An Open-Label, Multiday, Repeated Dose Clinical Trial	Orthopaedic (Total hip and knee arthroplasty), General surgery	947	Evaluate the safety of hydroxypropyl -b- cyclodextrin (HPbCD) diclofenac		HPBCD diclofenac	37,5mg/6h	None	5 days	30-37 days
Gong 2013[13]	Effects of combined application of muscle relaxants and celecoxib administration after total knee arthroplasty (TKA) on early recovery: a randomized, double-blind, controlled study	Total knee arthroplasty	147	Pain scores on postoperative 1st, 3rd, 7th, 11th, 14th days	Morphine consumption, active range of motion, relative complications	Celecoxib and hydrochlorid	300mg/12h	Placebo	14 days	14 days
						Celecoxib	300mg/12h			

Sivrikoz 2014[14]	Perioperative dexketoprofen or lornoxicam administration for pain management after major orthopedic surgery: a randomized, controlled study	Total hip and knee arthroplasty	120	Pain level and morphine consumption		Dexketo-profen	50mg/12h	Placebo	24h	24h
						Lornoxicam	8mg/12h			
Mochizuki 2016[15]	Tramadol hydrochloride/acetamin ophen combination versus non-steroidal anti-inflammatory drug for the treatment of perioperative pain after total knee arthroplasty: a prospective, randomized, open-label clinical trial	Total knee arthroplasty	280	Pain visual analog scale (VAS) change from baseline (PO day 2) and PO day 4, day 7, day 10, and day 14.	Number of days until the patient achieved independence from cane walking	Loxoprofen	180mg/24h	Tramadol and paraceta-mol	12 days	14 days
McQuay 2016[16]	Randomized clinical trial of dexketoprofen/ tramadol 25 mg/75 mg in moderate-to-severe pain after total hip arthroplasty	Total hip arthroplasty	641	Mean sum of pain intensity differences throughout 8 h after the first dose	Pain scores, mean sum pain intensity difference at rest, mean percentage of theoretical maximum sum pain intensity difference at rest, percentage of pain intensity responders and worst pain on movement	Dexketo-profen	25mg/8h	Placebo or tramadol	5 days	12 days
						Dexketo-profen and Tramadol	25 mg/8h			

Winkler 2016[17]	Perioperative blood loss and gastrointestinal tolerability of etoricoxib and diclofenac in total hip arthroplasty (ETO-DIC study): a single-center prospective double-blinded randomized controlled trial	Total hip arthroplasty	100	Total blood loss	Incidence of heterotopic ossification 6 months after THA, Analgesic efficacy of etoricoxib and diclofenac, Tolerability and rate of GI complications	Etoricoxib	90mg/24h	None	9 days	6 months
						Diclofenac	75mg/12h			
Gupta 2016[18]	A randomized trial comparing the safety and efficacy of intravenous ibuprofen versus ibuprofen and acetaminophen in knee or hip arthroplasty	Total hip and knee arthroplasty	78	Pain score	Opioid requirements, quality of recovery scale, length of hospital stay, length of PACU stay, need for antiemetic medications and safety (incidence of treatment-emergent adverse events that included gastrointestinal symptoms)	Ibuprofen	800mg/6h	Ibuprofen and paraceta-mol	5 days	1-5 days

Liu 2018[19]	Preoperative celecoxib analgesia is more efficient and equally tolerated compared to postoperative celecoxib analgesia in knee osteoarthritis patients undergoing total knee arthroplasty: a randomized, controlled study	Total knee arthroplasty	226	Pain score	Active and passive flexional angles, morphine consumption, percentage of rescue use of pethidine, consumption of pethidine, adverse events	Celecoxib	400mg/6h		3 days	3 days
						Celecoxib	200 mg/12h			
Xiao 2019[20]	Pain management using perioperative administration of parecoxib for total hip arthroplasty: a randomized, double-blind, placebo-controlled trial	Total hip arthroplasty	141	Pain score and morphine consumption	Adverse events, number of days needed to accomplish straight leg raising, off bed exercise, days of hospital stay	Parecoxib	40mg/12h	Placebo	48h	2 days
Thybo 2019[21]	Effect of combination of paracetamol (acetaminophen) and ibuprofen vs either alone on patient-controlled morphine consumption in the first 24 hours after total hip arthroplasty – the PANSAID randomized clinical trial	Total hip arthroplasty	559	24-hour morphine consumption and proportion of patients with 1 or more serious adverse events within 90 days after surgery	Pain score, adverse events from 0 to 24h	Ibuprofen	400mg/6h	Paraceta-mol	24h	1 year

Zhuang 2020[22]	Postoperative intravenous parecoxib sodium followed by oral celecoxib post total knee arthroplasty in osteoarthritis patients (PIPFORCE): a multicentre, double-blind, randomised, placebo-controlled trial	Total knee arthroplasty	246	Cumulative opioid consumption at 2 weeks post operation	Pain relief, inflammation control and functional rehabilitation after TKA and determining the safety profiles of study and control regimens.	Parecoxib and Celecoxib	Parecoxib: 40mg/12h for 3 days *afterwards* Celecoxib: 200mg/12h for 6 weeks	Placebo	6 weeks	12 weeks
Berkowitz 2021[23]	Safety and efficacy of perioperative iv meloxinam for moderate to severe pain mangemange in TKA	Total knee arthroplasty	181	Opioid consumption 24h after end of surgery	Pain intensity. Opioid-free subjects at the end of surgery to 24 hours. Time from end of surgery to first use of IV opioid as rescue medication. Questionnaire of 7-item patient-reported Overall Benefit of Analgesia Svore (OBAS). Incidence of adverse events. Laboratory values and vital signs. Wound healing satisfaction	Meloxicam	30 mg/24h	Placebo	1-4 days	30 days

Gottlieb 2021[24]	Extending the safety profile of the post-operative administration of an intravenous acetaminophen/ibuprofen fixed dose combination: An open-label, multi-center, single arm, multiple dose study	Orthopaedic (incl. total hip and knee arthroplasty), General, and Plastic surgery	233	Incidence of treatment-emergent adverse events associated with exposure to the FDC.	Time course of treatment-emergent adverse events, the incidence of treatment-related adverse events, treatment-emergent adverse events of interest (cardiovascular, gastrointestinal, renal, hepatic, administration site conditions and bleeding-related events), changes in vital sign measurements, changes in clinical laboratory values, and patient's global evaluation of the study drug.	Ibuprofen and paracetamol	300mg/6h	None	2-5 days	9-12 days
Hu, 2021[25]	Evaluation of analgesic effect, joint function recovery and safety of meloxicam in knee osteoarthritis patients who receive total knee arthroplasty - A randomized, controlled, double-blind study	Total knee arthroplasty	128	Pain score at 6h, 12h and day 1-2-3-7	Morphine consumption, patient satisfaction, knee function recovery, adverse events	Meloxicam	15mg bolus and 7,5mg/12h	Placebo	72h	3 months
Lubis, 2021[26]	The use of combination paracetamol and ibuprofen in postoperative pain after total knee arthroplasty: a randomized controlled trial	Total knee arthroplasty	36	Morphine consumption 24h after surgery	Pain intensity, walking test	Ibuprofen and paracetamol	800mg/6h	Paraceta-mol	24h	24h
						Ibuprofen	800mg/6h			

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Appendix 3

Summary of product characteristics of ibuprofen in original language

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

21. september 2021

PRODUKTRESUMÉ

for

Ibumetin, filmovertrukne tabletter 400 mg og 600 mg

0. D.SP.NR.
3916

1. LÆGEMIDLETS NAVN
Ibumetin

2. KVALITATIV OG KVANTITATIV SAMMENSÆTNING
Ibuprofen 400 mg og 600 mg
Hjælpestof, som behandleren skal være opmærksom på:

Ibumetin 400 mg indeholder 40 mg lactosemonohydrat.
Ibumetin 600 mg indeholder 60 mg lactosemonohydrat.

Alle hjælpestoffer er anført under pkt. 6.1

3. LÆGEMIDDELFORM

Filmovertrukne tabletter

Udseende:

400 mg: Hvid, hvælvet oval tablet med delekærv.

600 mg: Hvid, oval tablet med delekærv.

4. KLINISKE OPLYSNINGER

4.1 Terapeutiske indikationer

Reumatiske sygdomme og andre inflammatoriske lidelser. Svær dysmenoré. Svage smerter.

4.2 Dosering og indgivelsesmåde

Voksne

Reumatiske sygdomme og andre inflammatoriske lidelser: Maksimalt 1800 mg i døgnet fordelt på 3-4 doser. Doseringen kan øges op til 2400 mg pr. døgn, dog kun til kortere tids anvendelse (4-6 uger).

Pædiatrisk population

20-40 mg/kg/døgn fordelt på 3 doser.

Nedsat leverfunktion

Dosisjustering er ikke nødvendig ved let nedsat leverfunktion, men ibuprofen bør anvendes med forsigtighed.

Nedsat nyrefunktion

Dosisjustering er ikke nødvendig ved let nedsat nyrefunktion, men ibuprofen bør anvendes med forsigtighed.

Ældre

Dosisjustering er ikke nødvendig, men ibuprofen bør anvendes med forsigtighed, da gastrointestinale bivirkninger kan være mere alvorlige i denne patientgruppe (se pkt. 4.4).

Der bør anvendes den laveste effektive dosis i den kortest mulige tid, som er nødvendig for at lindre symptomerne (se pkt. 4.4).

4.3 Kontraindikationer

Ibumetin er kontraindiceret til patienter med:

- overfølsomhed over for det aktive stof eller over for et eller flere af hjælpestofferne.
- alvorlig hjerteinsufficiens (NYHA-klasse IV)
- gastrointestinal blødning eller perforation i anamnesen i forbindelse med NSAID-behandling
- bronkospasmer, angioødem, astma, rhinitis eller urticaria i anamnesen efter indtagelse af acetylsalicylsyre eller andre NSAID
- aktivt eller tilbagevendende ulcerøs colitis, Crohns sygdom, aktivt eller tilbagevendende gastrointestinalt ulcus eller gastrointestinal blødning (dvs. to eller flere særskilte episoder af diagnosticeret ulcus eller blødning)
- øget blødningstendens (f.eks. svær trombocytopeni)
- svær leverinsufficiens
- svær nyreinsufficiens (glomerulusfiltration under 30 ml/minut)
- graviditet i 3. trimester.

4.4 ærlige advarsler og forsigtighedsregler vedrørende brugen

Samtidig brug af ibuprofen og acetylsalicylsyre eller andre NSAID-præparater inklusive selektive cyclooxygenase-2 hæmmere bør undgås (se pkt. 4.5).

Ibumetin bør anvendes med forsigtighed til astmatikere, idet ibuprofen kan forårsage bronkospasmer.

Symptomerne behandles i så kort tid og med så lav dosis som muligt for at minimere bivirkningerne af Ibumetin (se pkt. 4.2 samt nedenstående om gastrointestinale og kardiovaskulære risici).

Maskering af symptomer på underliggende infektioner

Ibumetin kan maskere symptomer på infektion, hvilket kan medføre forsinket påbegyndelse af relevant behandling og dermed en forværring af infektionens udfald. Dette er observeret ved bakteriel samfundserhvervet pneumoni og bakterielle komplikationer til varicella. Når Ibumetin gives som feber- eller smertestillende middel i forbindelse med infektion, bør infektionen overvåges. Hvis patienten ikke er indlagt på hospital, bør vedkommende kontakte sin læge, hvis symptomerne varer ved eller forværres.

Ældre

Ældre får oftere bivirkninger ved brug af NSAID, især gastrointestinal blødning og perforation, som kan være fatale.

Gastrointestinale påvirkninger

Der er rapporteret gastrointestinale blødninger, ulcerationer eller perforationer, som kan være fatale, ved behandling med ibuprofen og alle typer af NSAID-præparater. Disse bivirkninger er opstået på ethvert tidspunkt under behandlingen, med eller uden advarende symptomer eller alvorlige gastrointestinale fortilfælde.

Risikoen for gastrointestinal blødning, ulceration eller perforation er øget ved højere doser af NSAID, hos patienter med ulcus i anamnesen (særligt med samtidig blødning eller perforation) (se pkt. 4.3) og hos ældre. Disse patienter bør indlede behandlingen med den lavest mulige dosis.

Kombinationsbehandling med slimhindebeskyttende midler (f.eks. misoprostol eller protonpumpehæmmere) bør overvejes til disse patienter samt til patienter med behov for samtidig behandling med lave doser acetylsalicylsyre eller andre stoffer, som sandsynligt vil øge risikoen for gastrointestinale bivirkninger (se nedenstående og pkt. 4.5).

Patienter, særligt ældre, med gastrointestinal toksicitet i anamnesen bør rapportere alle usædvanlige abdominale symptomer (særligt gastrointestinal blødning) i særdeleshed i behandlingens startfase. Patienter, der samtidig bruger medicin, som øger risikoen for gastrointestinalt ulcus eller blødning, såsom orale kortikosteroider, antikoagulantia som warfarin, selektive serotoningenoptagelseshæmmere (SSRI) eller trombocythæmmende midler som acetylsalicylsyre, bør rådes til forsigtighed (se pkt. 4.5).

Hvis gastrointestinal blødning eller ulceration opstår hos patienter i behandling med ibuprofen skal behandlingen seponeres.

Forsigtighed tilrådes ved behandling af patienter med gastrointestinale lidelser i anamnesen (særligt colitis ulcerosa, Crohns sygdom), da behandling med NSAID-præparater kan forværre disse tilstande (se pkt. 4.8).

Kardiovaskulære og cerebrovaskulære påvirkninger

Patienter med hypertension og/eller mild til moderat hjerteinsufficiens i anamnesen bør monitoreres og rådgives fyldestgørende, da væskeretention og ødemer er rapporteret i forbindelse med brug af NSAID.

Kliniske studier antyder, at der ved brug af ibuprofen, specielt i høje doser (2400 mg daglig), kan være forbundet med en let forøget risiko for arterielle tromboser (f.eks. myokardieinfarkt eller apopleksi). Samlet set tyder til epidemiologiske studier ikke på, at lavdosis ibuprofen (f.eks. ≤ 1200 mg daglig) er forbundet med en forøget risiko for arterielle trombotiske hændelser.

Patienter med ukontrolleret hypertension, kongestiv venstresidig hjerteinsufficiens (NYHA II-III), bekræftet iskæmisk hjertesygdom, perifer arteriesygdom og/eller cerebrovaskulær sygdom bør kun behandles med ibuprofen efter nøje overvejelse, og høje doser (2400 mg/dag) bør undgås.

Initiering af langvarig behandling hos patienter med risikofaktorer for kardiovaskulære hændelser (f.eks. hypertension, hyperlipidæmi, diabetes mellitus, rygning) skal også nøje overvejes, særligt hvis høje ibuprofendoser (2400 mg/dag) er nødvendige.

Svære hudreaktioner

Der er rapporteret om sjældne tilfælde af alvorlige hudreaktioner, indimellen med dødelig udgang, herunder eksfoliativ dermatitis, Stevens-Johnson syndrom og toksisk epidermal nekrolyse, ved anvendelse af NSAID'er (se pkt. 4.8). Patienterne har formentlig højere risiko for at få disse reaktioner tidligt i behandlingsforløbet, idet reaktionen i de fleste tilfælde opstår inden for den første måned af behandlingen. Der er rapporteret om akut generaliseret eksantematøs pustulose (AGEP) i forbindelse med ibuprofen-holdige lægemidler. Ibuprofen bør seponeres ved de første tegn og symptomer på svære hudreaktioner, f.eks. hududslæt, læsioner i slimhinderne eller andre tegn på overfølsomhed.

I enkeltstående tilfælde kan infektion med varicella medvirke til komplikationer af alvorlige hud- og bløddelsinfektioner.

Alvorlige, akutte overfølsomhedsreaktioner (f.eks. anafylaktisk chok) er kun set i meget sjældne tilfælde. Hvis der viser sig tidlige tegn på en overfølsomhedsreaktion efter indtagelse/administration af ibuprofen, skal behandlingen seponeres. Der skal igangsættes nødvendige medicinske tiltag i overensstemmelse med symptomerne af specialiseret personale.

Fertilitet

Anvendelsen af ibuprofen kan reducere fertiliteten og bør derfor ikke anvendes til kvinder, som ønsker at blive gravide. For kvinder, som har problemer med at blive gravide eller bliver undersøgt for infertilitet, bør seponering af ibuprofen overvejes (se pkt. 4.6).

Medicinoverforbrugshovedpine

Ved længerevarende brug af enhver type smertestillende hovedpinemedicin kan hovedpine blive værre og hyppigere (medicinoverforbrugshovedpine). Hvis denne tilstand udvikles eller mistænkes, skal lægen kontaktes med henblik på afbrydelse af hovedpinebehandlingen. Medicinoverforbrugshovedpine bør mistænkes hos patienter med hyppige eller daglige hovedpineanfald på trods af (eller på grund af) regelmæssig brug af smertestillende medicin.

Virkning på nyrefunktionen

Der bør udvises særlig forsigtighed, når behandling med Ibumetin startes op hos stærkt dehydrerede patienter.
Der er en risiko for nedsat nyrefunktion hos dehydrerede børn og unge.

Ibumetin bør gives med forsigtighed til patienter med nedsat nyrefunktion, da anvendelse af NSAID kan resultere i forværring af nyrefunktionen. Dosis bør være så lav som muligt, og nyrefunktion bør monitoreres.

Som for andre NSAID kan langtidsbehandling med Ibumetin resulterer i papillær nekrose og andre patologiske ændringer i nyren. Nyretoksicitet er også set hos patienter, hos hvem prostaglandiner fra nyren har en kompensatorisk rolle i vedligeholdelsen af nyrens gennemblødning. Hos disse patienter, kan administration af non-steroide anti-inflammatoriske lægemidler forårsage en dosisafhængig reduktion i dannelsen af prostaglandiner og sekundært i nyrens blodgennemstrømning, som kan fremskynde nedbrydning af nyren. De patienter, som har størst risiko for denne reaktion, er patienter med svækket nyrefunktion, hjerteinsufficiens, svækket leverfunktion, patienter i behandling med diuretika og ACE-hæmmere samt ældre. Ophør med behandling med non-steroide anti-inflammatoriske lægemidler efterfølges normalt med bedring til det stadie, som fandtes inden behandlingen.

Ibuprofens prostaglandinhæmmende effekt kan resultere i let nedsat nyrefunktion på grund af nedsat renal blodgennemstrømning, der dog normalt er reversibel. Patienter med reno-vaskulær sygdom, leversygdom, hjerteinsufficiens, diabetes mellitus, SLE, i behandling med diuretika eller nefrotoksiske lægemidler, samt ældre har størst risiko for at udvikle akut nyresvigt og bør derfor have foretaget en nyrefunktionsundersøgelse før og under behandling med ibuprofen.

Nedsat leverfunktion

Ibumetin skal anvendes med forsigtighed til patienter med nedsat leverfunktion, da levertoksicitet kan forekomme.

Som for andre NSAID'er er der observeret sjældne tilfælde af aseptisk meningitis, sandsynligvis har patienter med lupus og lignende bindevævssygdomme en højere risiko, men aseptisk meningitis er også rapporteret hos patienter, der ikke havde nogen bagvedliggende kronisk sygdom.

Hæmotologiske virkninger

Ibumetin kan, som andre NSAID'er, forhindre koagulation og er vist at kunne forlænge blødningstiden hos normale individer.

Ibuprofen kan som andre NSAID'er maskere tegn på infektion.

Ibuprofen virker febernedsættende.

Ibuprofen bør anvendes med forsigtighed til patienter

- i behandling med methotrexat (se pkt. 4.5)
- i behandling med lithium (se pkt. 4.5)
- i behandling med ciclosporin eller tacrolimus (se pkt. 4.5)
- i behandling med diuretika (se pkt. 4.5).

Ibumetin indeholder lactose

Bør ikke anvendes til patienter med hereditær galactoseintolerans, total lactasemangel eller glucose/galactosemalabsorption.

Ibumetin indeholder mindre end 1 mmol (23 mg) natrium pr. dosis, dvs. den er i det væsentlige natriumfri.

4.5 Interaktion med andre lægemidler og andre former for interaktion

Følgende kombinationer bør undgås:

Antihypertensionsbehandling, beta-blokkere og diuretika

NSAID kan reducere nedsætte effekt af antihypertensionsbehandling, f.eks. ACE-hæmmer, beta-blokkere og diuretika. Diuretika kan også øge risikoen for NSAID'er nefrotoksicitet.

Acetylsalicylsyre

Mulig mekanisme: Kompetitiv binding til COX-1 bindingsstedet på blodpladerne.

Effekt: Nedsat antikoagulerende virkning af acetylsalicylsyre.

Som for andre NSAID-præparater, bør Ibumetin og acetylsalicylsyre ikke administreres samtidig, idet den mulige risiko for bivirkninger forøges.

Eksperimentelle data tyder på, at ibuprofen muligvis kompetitivt hæmmer virkningen af lave doser acetylsalicylsyre på trombocytaggregation ved samtidig administration. Der er usikkerhed vedrørende ekstrapolation af disse data til den kliniske situation, men muligheden for, at regelmæssig langvarig behandling med ibuprofen kan nedsætte den kardioprotektive virkning af lavdosis acetylsalicylsyre, kan ikke udelukkes. En klinisk relevant virkning ved lejlighedsvis brug af ibuprofen anses ikke for at være sandsynlig (se pkt. 5.1).

COX-2 hæmmere og andre NSAID-præparater

Samtidig anvendelse med andre NSAID-præparater, inklusive cyclooxygenase-2-selektive hæmmere bør undgås på grund af den mulige additive effekt.

Digoxin

NSAID-præparater kan forværre hjerteinsufficiens, reducere den glomerulære filtreringshastighed og øge plasmaniveauet for hjerteglykosider.

Methotrexat

Mulig mekanisme: Nedsat renal methotrexatclearance.

Effekt: Methotrexattoksicitet (leukæmi, trombocytopeni, anæmi, nefrotoksicitet, slimhindeforandringer (se pkt. 4.4)).

Samtidig anvendelse af følgende kan anvendes under visse forholdsregler og dosisjusteringer

Antikoagulantia
NSAID-præparater kan forstærke effekten af antikoagulantia (se pkt. 4.4). Øget monitorering af koagulationen anbefales i tilfælde af samtidig behandling.

W*arfarin, phenprocoumon*
Mulig mekanisme: Reducerer thrombindannelsen, der resulterer i indirekte reduktion af blodpladeaktiviteten.
Effekt: Øget risiko for blødning.

Heparin
Mulig mekanisme: Reducerer thrombindannelsen, der resulterer i indirekte reduktion af blodpladeaktiviteten.
Effekt: Øget risiko for blødning.

ACE hæmmere
Mulig mekanisme: Hæmning af prostaglandinsyntesen.
Effekt: Nedsat effekt af ACE-hæmmere.

Furosemid
Mulig mekanisme: Hæmning af den proximale tubulære udskillelse af furosemid.
Effekt: Nedsætter furosemids diuretiske effekt. Forsigtighed anbefales ved samtidig brug (se pkt. 4.4). Samtidig indtagelse kan øge risikoen for svækkelse af nyrefunktion.

Thiaziddiuretika
Mulig mekanisme: Nedsat renal produktion af prostaglandin.
Effekt: Nedsat diuretisk og antihypertensiv effekt. Bør anvendes med forsigtighed ved samtidig brug (se pkt. 4.4).

β-blokkere
Mulig mekanisme: Nedsat produktion af vasodilaterende og renale prostaglandiner.
Effekt: Nedsat antihypertensiv effekt.

Kortikosteroider
Mulig mekanisme: Ukendt.
Effekt: Øget risiko for gastrointestinalt ulcus eller blødning.

Lithium

Mulig mekanisme: Nedsætter den renale clearance af lithium.
Effekt: Øget risiko for lithiumtoksicitet (svaghed, rysten, ekstrem tørst, forvirring se pkt. 4.4).

Colestyramin
Samtidig brug af ibuprofen og colestyramin kan reducere absorptionen af ibuprofen i mave-tarm-kanalen. Dog er den kliniske signifikans ukendt.

Ciclosporin
Mulig mekanisme: Forøger plasmakoncentrationen af ciclosporin.
Effekt: Øget risiko for ciclosporintoksicitet renal-dysfunktion, cholestasis, paræstesi (se pkt. 4.4).

Trombocythæmmende midler og selektive serotonin genoptagelseshæmmere (SSRI)
Mulig mekanisme: Ukendt.

Effekt: Øget risiko for blødning f.eks. fra gastrointestinalkanalen (se pkt. 4.4). Denne risiko øges ved kombinationsbehandling.

Abciximab, tirofiban, integrelin
Mulig mekanisme: Øget hæmning af blodpladeaktiviteten (glycoprotein IIb/IIIa inhibitor).
Effekt: Øget risiko for blødning.

Clopidogrel
Mulig mekanisme: Øget hæmning af blodpladeaktiviteten (blodplade-ADP-receptor-antagonist).
Effekt: Øget risiko for blødning.

Hvis to eller flere af de ovenfor nævnte stoffer indgives sammen med ibuprofen kan det medføre en synergieffekt med øget hæmning af blodpladeaktiviteten og øget blødningstendens til følge.

Rivaroxaban og dabigatran
Samtidig administration af ibuprofen og faktor Xa-hæmmere og trombinhæmmere øger risikoen for blødning. Hvis to eller flere af de ovenfor nævnte lægemidler indgives sammen med ibuprofen, kan det medføre en synergieffekt med øget hæmning af blodpladeaktiviteten og øget blødningstendens til følge.

Mifepriston
Et fald i effekten af lægemidlet kan teoretiske forekomme grundet NSAIDs antiprostalglandine egenskaber. Begrænset evidens tyder på, at samtidig administration af NSAID på dagen for prostaglandin administration ikke har en negativ indflydelse af mifepriston eller prostaglandins effekt på modning af cervix eller uterin kontraktilitet og det mindsker ikke den kliniske effekt af medicinsk svangerskabsafbrydelse.

Quinolon
Data fra dyreforsøg tyder på, at NSAID kan øge risikoen for quinolon antibiotika associerede kramper. Patienter, der tager NSAID og quinolon antibiotika samtidig, kan have en øget risiko for at udvikle kramper.

Sulfonylurea
NSAID'er kan forstærke effekten af lægemidler med sulfonylurea. Sjældne tilfælde af hypoglykæmi er set hos patienter der bruger ibuprofen sammen med sulfonylurea.

Tacrolimus
Mulig mekanisme: Ukendt.
Effekt: Øget risiko for tacrolimus-nefrotoksicitet. Bør anvendes med forsigtighed ved samtidig brug (se pkt. 4.4).

Zidovudin
Der er påvist en øget risiko for ledblødning og hæmatom hos HIV-positive bløderpatienter, der tager zidovudin og ibuprofen samtidigt.

CYP2C9 hæmmere
Samtidig brug af ibuprofen og CYP2C9 hæmmere kan øge eksponeringen for ibuprofen (CYP2P9 substrat). I et studie med voriconazol og fluconazol (CYP2C9 hæmmere) blev en øget eksponering af S (+) - ibuprofen på 80 til 100 % påvist. Reduktion af ibuprofen dosis bør overvejes ved samtidig administration af potente CYP2C9 hæmmere, især når høje doser af ibuprofen gives sammen med voriconazol eller fluconazol.

Aminoglykosider
NSAID-præparater kan nedsætte udskillelse af aminoglykosider.

Naturlægemidler
Ginkgo biloba kan forøge risikoen for blødning med NSAID-præparater.

Alkohol
Øget risiko for forekomst og potentiering af gastrointestinal blødning samt mulig potentiering af virkningerne på centralnervesystemet ved samtidig administration med alkohol (kombinationen bør undgås).

4.6 Graviditet og amning

Graviditet

Tredje trimester
Prostaglandinsyntesehæmmere som f.eks. NSAID er kontraindiceret under tredje trimester af graviditeten, da prostaglandinsyntesehæmmere under tredje trimester af graviditeten kan udsætte fosteret for:

- kardiopulmonær toksicitet (for tidlig lukning af ductus arteriosus og pulmonær hypertension)
- renal dysfunktion som kan lede til nyresvigt og dermed en reduceret mængde fostervand,
- og ved graviditetens slutning kan prostaglandinsyntesehæmmere udsætte
- moren og det nyfødte barn for:
- forlænget blødningstid som følge af en nedsat aggregationsevne for trombocytterne, hvilket kan forekomme selv ved meget lave doser
- hæmning af livmoderkontraktioner, hvilket kan resultere i for sen eller forlænget fødsel.

Første og andet trimester
Prostaglandinsyntesehæmmere bør kun anvendes på tvingende indikation under første og andet trimester af graviditeten, og dosis bør være så lav og behandlingstiden så kort som muligt.

Fertilitet

NSAID bør ikke anvendes til kvinder, som ønsker at blive gravide, da prostaglandinsyntesehæmmere menes at kunne nedsætte fertiliteten.
Hvis behandling med NSAID er nødvendig, bør behandlingen være så kortvarig og i så lave doser som muligt. Virkningen på fertiliteten er reversibel.

NSAID'ers hæmning af prostaglandinsyntesen kan have en skadelig indvirkning på graviditeten og/eller den embryonale/føtale udvikling. Data fra epidemiologiske studier tyder på en øget risiko for spontan abort og for medfødte misdannelser i barnets hjerte samt gastroschisis ved brug af prostaglandinsyntesehæmmere under den tidlige graviditet. Den absolutte risiko for medfødte misdannelser i hjertet stiger fra mindre end 1 % til cirka 1,5 %. Risikoen menes at stige med øget dosis og behandlingsvarighed. Hos dyr har administration af prostaglandinsyntesehæmmere vist sig at medføre en øget hyppighed af præ- og postimplantationstab samt embryo-/fosterdød. Endvidere er der fundet en øget forekomst af flere misdannelser, herunder kardiovaskulære hos dyr, der har været eksponeret for en prostaglandinsyntesehæmmer under den organudviklende periode.

Amning

Ibumetin kan anvendes i ammeperioden.
Ibuprofen passerer i små mængder over i modermælken. Koncentrationen i modermælken er < 1 % af koncentrationen i plasma.

Selvom der ikke foreligger dokumentation om bivirkninger hos det ammede barn, bør der foretages en risk/benefit-vurdering, da spædbørn og børn er særlig følsomme for ibuprofens virkning.

4.7 Virkninger på evnen til at føre motorkøretøj eller betjene maskiner
Ikke mærkning.
Ibumetin kan især ved starten af behandlingen og ved øgning af dosis give svimmelhed og træthed, som kan påvirke evnen til at føre motorkøretøj eller betjene maskiner i mindre eller moderat grad.
Opstår der bivirkninger såsom synsforstyrrelse og svimmelhed bør opmærksomhedskrævende aktiviteter undgås som at føre motorkøretøj og betjene maskiner eller farligt værktøj.

4.8 Bivirkninger

De mest almindelige bivirkninger er gastrointestinalt relaterede. I kontrollerede kliniske studier rapporterer mellem 4 % og 36 % af patienterne én eller flere gastrointestinale gener. Ved korttidsbehandling med døgndoser op til 1200 mg ses en lavere hyppighed af bivirkninger.

Der kan forekomme peptisk ulcus, perforation eller gastrointestinal blødning, som kan være fatal, især hos ældre (se pkt. 4.4).

Frekvens Organklasse	Meget almindelig (≥1/10)	Almindelig – meget almindelig (>1/100)	Almindelig (≥1/100 og <1/10)	Ikke almindelig (≥1/1000 og <1/100)	Sjælden (≥1/10.000 og <1/1000)	Meget sjælden (<1/10.000)	Ikke kendt (kan ikke estimeres ud fra forhånden værende data)
Hjerte				Hjerteinsufficiens (hos patienter med begrænset hjertefunktion).			

Frekvens Organklasse	Meget almindelig (≥1/10)	Almindelig – meget almindelig (>1/100)	Almindelig (≥1/100 og <1/10)	Ikke almindelig (≥1/1000 og <1/100)	Sjælden (≥1/10.000 og <1/1000)	Meget sjælden (<1/10.000)	Ikke kendt (kan ikke estimeres ud fra forhånden værende data)
Blod og lymfesystem				Agranulocytose, pancytopeni, trombocytopeni, aplastisk og hæmolytisk anæmi, neutropeni, eosinofili, koagulationsforstyrrelser, aplasi af de hvide blodlegemer.			
Nervesystemet			Mild og forbigående hovedpine, svimmelhed.	Paræstesier.	Sløvhed, ekstrapyramidale gener.		
Øjne				Synsforstyrrelser (sløret syn, ændret farveopfattelse, nedsat syn, synsfelt defekter, scotoma, amblyopia, dobbeltsyn, iridocyclitis).	Optisk neuritis.		

Frekvens Organklasse	Meget almindelig (≥1/10)	Almindelig – meget almindelig (>1/100)	Almindelig (≥1/100 og <1/10)	Ikke almindelig (≥1/1000 og <1/100)	Sjælden (≥1/10.000 og <1/1000)	Meget sjælden (<1/10.000)	Ikke kendt (kan ikke estimeres ud fra forhånden værende data)
Øre og labyrint			Tinnitus.	Påvirkning af hørelsen.			
Luftveje, thorax og mediastinum				Bronkospasme, astmatisk anfald, forværring af astma, dyspnø.		Eksacerbation af bronkospasme.	
Mave-tarmkanalen	Dyspepsi, diarré.	Gastrointestinal blødning, hæmatemesis, melæna, mavesmerter, flatulens.	Gastrointestinale gener som kvalme, opkastninger, smerter i epigastriet, abdominalt ubehag, fordøjelsesbesvær, forstoppelse, abdominale kramper.	Gastrisk eller duodenale ulcera med blødning og/eller perforation, colitis, inflammtoriske tarmsygdomme, ulcøs stomatitis, gastritis (kvalme, opkastninger, mavesmerter), halsbrand.		Pancreatitis, forværring af colitis og Crohns sygdom.	
Nyrer og urinveje			Øget ureakoncentrationer i serum, øget serumkreatinin.	Akut nyreinsufficiens, interstitiel nefritis, nefrotisk syndrom.	Papilnekrose, membranøs nefropati.	Nedsat urinstof udskillelse.	

Frekvens Organklasse	Meget almindelig (≥1/10)	Almindelig – meget almindelig (>1/100)	Almindelig (≥1/100 og <1/10)	Ikke almindelig (≥1/1000 og <1/100)	Sjælden (≥1/10.000 og <1/1000)	Meget sjælden (<1/10.000)	Ikke kendt (kan ikke estimeres ud fra forhånden værende data)
Hud og subkutant væv			Exantem.	Urticaria, pruritus, purpura, fotosensitivitet.	Bulløst exantem.	Toksisk epidermal nekrose (TEN), morbiliformt udslæt, erythema nodosum, erythema multiforme, Stevens-Johnson syndrom, hårtab, sygdomme i hår og negle, dermatitis herpetiformis.	Lægemiddelreaktion med eosinofili og systemiske symptomer (DRESS). Akut generaliseret eksantematøs pustulose (AGEP).
Metabolisme og ernæring					Hyponatriæmi.		

Frekvens Organklasse	Meget almindelig (≥1/10)	Almindelig – meget almindelig (>1/100)	Almindelig (≥1/100 og <1/10)	Ikke almindelig (≥1/1000 og <1/100)	Sjælden (≥1/10.000 og <1/1000)	Meget sjælden (<1/10.000)	Ikke kendt (kan ikke estimeres ud fra forhånden værende data)
Infektioner og parasitære sygdomme				Rinit.	Aseptisk meningitis (nakkestivhed, hovedpine, kvalme, opkastning, feber eller desorientering hos patienter med eksisterende autoimmune sygdomme).		Forværring af infektionsrelaterede inflammationer (f.eks. udvikling af nekrotiserende fasciitis) i forbindelse med brug af NSAID. Dette hænger muligvis sammen med NSAID'ers virkningsmekanisme.
Vaskulære sygdomme				Hypertension.		Vaskulitis.	

Frekvens Organklasse	Meget almindelig (≥1/10)	Almindelig – meget almindelig (>1/100)	Almindelig (≥1/100 og <1/10)	Ikke almindelig (≥1/1000 og <1/100)	Sjælden (≥1/10.000 og <1/1000)	Meget sjælden (<1/10.000)	Ikke kendt (kan ikke estimeres ud fra forhånden værende data)
Almene symptomer og reaktioner på administrationsstedet		Træthed.	Væskeretention, ødemer.		Kulderystelser, drug fever.		
Immunsystemet				Anafylaksi/anafylak-toide reaktioner, angioødem, generaliseret hypersensitivitet.		Anafylaktisk chok.	
Lever og galdeveje				Hepatitis, gulsot, betydelig forhøjelse af leverparametre (ASAT og ALAT).	Levertoksicitet.	Leverskader (specielt i langtidsbehandling), leversvigt.	

Frekvens Organklasse	Meget almindelig (≥1/10)	Almindelig – meget almindelig (>1/100)	Almindelig (≥1/100 og <1/10)	Ikke almindelig (≥1/1000 og <1/100)	Sjælden (≥1/10.000 og <1/1000)	Meget sjælden (<1/10.000)	Ikke kendt (kan ikke estimeres ud fra forhånden værende data)
Psykiske forstyrrelser				Hallucinationer, søvnløshed, nervøsitet, let rastløshed.	Depression, konfusion, koncentrationsbesvær, kognitiv dysfunktion.		

Beskrivelse af udvalgte bivirkninger

Kliniske studier antyder, at der er en lille forøget risiko for arterielle tromboser (f.eks. myokardieinfarkt eller apopleksi) ved brug af ibuprofen, specielt i høje doser (2400 mg dagligt) og ved langvarig behandling (se pkt. 4.4).

I enkeltstående tilfælde kan infektion med varicella medvirke til komplikationer af alvorlige hud- og bløddelsinfektioner (se også "Infektioner og parasitære sygdomme").

Indberetning af formodede bivirkninger
Når lægemidlet er godkendt, er indberetning af formodede bivirkninger vigtig. Det muliggør løbende overvågning af benefit/risk-forholdet for lægemidlet. Sundhedspersoner anmodes om at indberette alle formodede bivirkninger via:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Websted: www.meldenbivirkning.dk

4.9 Overdosering

Toksicitet

Toksiciteten af ibuprofen afhænger af dosis og tiden siden indtagelsen. Hvert enkelt tilfælde skal bedømmes individuelt, da der er stor forskel i den enkeltes respons.
Ved doser >80-100 mg/kg: risiko for symptomer.
Ved doser >200 mg/kg: risiko for alvorlige symptomer, dog individuelle variationer.

560 mg/kg til børn på 15 måneder: alvorlig toksicitet.
3,2 g til 6-årige børn: let til moderat toksicitet.
2,8-4 g til 1½ år og 6 g til 6-årige: alvorlig toksicitet.
8 g til børn på 16 år: nyrepåvirkning.
12 g i kombination med alkohol til unge: akut tubulær nekrose.

Symptomer

De hyppigste symptomer er mavesmerter, kvalme, opkastning, letargi og sløvhed. Andre CNS-relaterede symptomer er svimmelhed, hovedpine, tinnitus, generel CNS-hæmning og kramper. Sjældent ses metabolisk acidose, respirationsdepression, koma, påvirkning af leverfunktionen, hypernatriæmi, akut nyresvigt, hæmaturi og apnø (især hos meget små børn). Kardiovaskulær toksicitet, inklusive hypotension, bradykardi, takykardi og atrieflimmer er også rapporteret. Ved alvorlig forgiftning kan metabolisk acidose forekomme.

Behandling

Der findes ingen specifik antidot. Ventrikelaspiration og symptomatisk og understøttende behandling anbefales. Eventuelt korrektion af elektrolytforstyrrelser.

4.10 Udlevering

B

5. FARMAKOLOGISKE EGENSKABER

Terapeutisk klassifikation

M 01 AE 01 – Non-steroide antiinflammatoriske og antirheumatiske midler, propionsyre-derivater

5.1 Farmakodynamiske egenskaber

Ibuprofen tilhører gruppen af NSAID. Ibuprofen er et 2-propionsyrederivat. Ibuprofen virker antiinflammatortisk, analgetisk, antipyretisk og forlænger blødningstiden.

Virkningsmekanismen for antiinflammatoriske stoffer og den analgetiske effekt beror på en hæmning af prostaglandinsyresyntesen via en hæmning af enzymet cyklooxygenase. Virkningsmekanismen endnu ikke fuldt klarlagt, idet nyere forskning tyder på, at NSAID'er også virker på spinale og centrale mekanismer, der spiller en rolle i transmissionen og perceptionen af smerten samt i den centrale regulering af inflammationen.

Ibuprofen blokerer for dannelsen af prostaglandin $E_{2\alpha}$, der udløser hyperkontraktabiliteten i uterus ved dysmenorré. Ibuprofen nedsætter trombocytternes aggregationsevne. Ibuprofen hæmmer den renale prostaglandinsyntese. Hos patienter med normal nyrefunktion har det ingen betydning. Derimod kan det hos patienter med kronisk nyreinsuffienciens, svær hjerteinsufficiens eller leverinsufficiens medføre akut nyreinsufficiens, væskeretention eller hjerteinsufficiens. Ibuprofen virker antipyretisk ved hæmning af syntesen af prostaglandin E_2 i cerebrospinalvæsken.

Eksperimentelle data tyder på, at ibuprofen muligvis kompetitivt hæmmer virkningen af lavdosis acetylsalicylsyre på trombocytaggregation ved samtidig administration. Nogle farmakodynamiske studier viser, at acetylsalicylsyres virkning på dannelsen af tromboxan eller trombocytaggregation blev nedsat ved administration af enkeltdoser af ibuprofen på 400 mg inden for 8 timer før eller 30 minutter efter en dosis acetylsalicylsyre (81 mg) med umiddelbar udløsning. Der er usikkerhed vedrørende ekstrapolation af disse data

til den kliniske situation, men muligheden for, at regelmæssig langvarig behandling med ibuprofen kan nedsætte den kardioprotektive virkning af lavdosis acetylsalicylsyre, kan ikke udelukkes. En klinisk relevant virkning ved lejlighedsvis brug af ibuprofen anses ikke for at være sandsynlig (se pkt. 4,5).

5.2 Farmakokinetiske egenskaber

Absorption
Ibuprofen absorberes hurtigt og fuldstændigt. Maksimal plasmakoncentration opnås efter 1-2 timer.

Distribution
Proteinbindingsgraden er ca. 99 % i terapeutiske doser. Fordelingsvolumen er omtrent 0,15 l/kg. Fordelingsforholdet mellem plasmakoncentrationen og ledvæsken er 0,4.

Metabolisme
Metaboliseres i leveren til inaktive hydroxy- og carboxymetabolitter.

Elimination
90 % af dosis udskilles renalt dels i fri form, dels konjugeret. En ringe del udskilles formentlig med galden. Eliminationen er fuldstændig efter 24 timer. Plasmahalveringstiden er omkring 2 timer.

Prækliniske sikkerhedsdata
I dyreforsøg med gentagen dosering af ibuprofen var den eneste gennemgående patologiske effekt gastrointestinal ulceration.

Der er ikke fundet tegn på carcinogenitet hos rotter. Reproduktionsstudier på hvide kaniner, i første del af graviditeten, har ikke vist relaterede abnormiteter; tilsvarende tilfredsstillende resultater er fundet i mus og rotter. Kulturer af lymfocytter fra reumatologiske patienter i behandling med ibuprofen viste ingen signifikant forøgelse af kromosomaberrationer.

6. FARMACEUTISKE OPLYSNINGER

6.1 Hjælpestoffer
Cellulose, mikrokrystallinsk (E 460), croscarmellosenatrium (E 468), hypromellose (E 464), kartoffelstivelse, lactosemonohydrat, magnesiumstearat (E 470b), propylenglycol (E 1520), silica, kolloid vandfri (E 551), talcum (E 553 b).

6.2 Uforligeligheder
Ikke relevant.

6.3 Opbevaringstid
5 år.

6.4 Særlige opbevaringsforhold
Ingen særlige opbevaringsbetingelser.

6.5 Emballagetyper og pakningsstørrelser
Tabletbeholder (plast) og blister.

6.6 Regler for destruktion og anden håndtering
Ingen særlige forholdsregler.

Ikke anvendt lægemiddel samt affald heraf bør destrueres i henhold til lokale retningslinjer.

7. INDEHAVER AF MARKEDSFØRINGSTILLADELSEN

Orifarm Healthcare A/S
Energivej 15
5260 Odense S

8. MARKEDSFØRINGSTILLADELSESNUMRE

400 mg: 10610
600 mg: 10611

9. DATO FOR FØRSTE MARKEDSFØRINGSTILLADELSE

22. oktober 1981

10. DATO FOR ÆNDRING AF TEKSTEN

21. september 2021

Appendix 4

Definition of components of the primary, secondary and explorative outcomes measurements

Table 3: Definition of components of the primary outcome

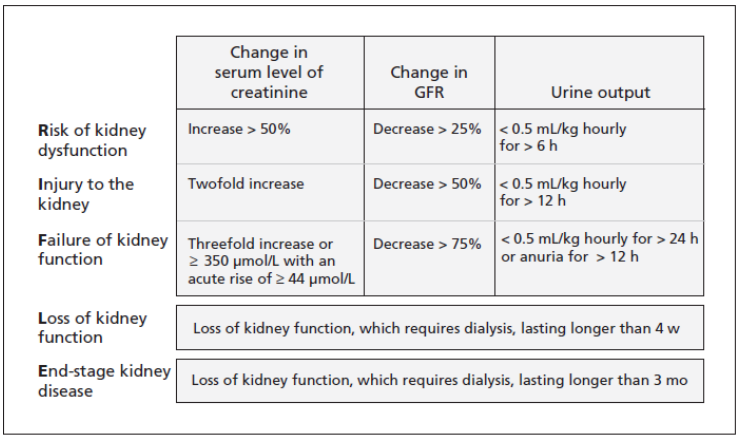
<table>
<tr><th></th><th>Definition</th><th>Data source</th></tr>
<tr><td>Death</td><td></td><td>“CPR-registeret” or medical record.</td></tr>
<tr><td>Acute myocardial infarction</td><td>Increased or decreased troponin and one of following: Symptoms of acute ischemia (chest pain, dyspnoea, acute heart insufficient, arrhythmia); ischemic ECG changes; visualisation of thrombosis or loss of viable myocardium via diagnostic imaging, e.g. angiography.[1]</td><td>“Landspatient registeret” or the medical record via diagnostic and procedure codes (SKS-codes)</td></tr>
<tr><td>Stroke</td><td>Rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours.[2] Transient cerebral ischemia (TCI) is defined as lasting less than 24 hours.[3]</td><td>“Landspatient registeret” or the medical record via diagnostic and procedure codes (SKS-codes)</td></tr>
<tr><td>Pulmonary embolism</td><td>Total or partially thrombotic occlusion of pulmonary artery.[4]</td><td>“Landspatient registeret” or the medical record via diagnostic and procedure codes (SKS-codes)</td></tr>
<tr><td>Deep venous thrombosis</td><td>Thrombosis of the deeper veins.[4]</td><td>“Landspatient registeret” or the medical record via diagnostic and procedure codes (SKS-codes).</td></tr>
<tr><td>Renal failure</td><td>RIFLE criteria:[5]
 

Figure 1: The RIFLE classification for acute renal failure.[5] The grade of injury or outcome is determined by either the serum level of creatinine or the rate of glomerular filtration (GFR), whichever indicates the more severe grade of renal failure.</td><td>“Landspatient registeret” or the medical record via diagnostic codes (SKS-codes) and via creatinine levels and/or urine output.</td></tr>
<tr><td>Major bleeding requiring</td><td>Bleeding requiring surgery or transfusion of ≥2 units of red blood cells (SAGM) or associated with a decrease in hemoglobin of ≥ 2.0 g/L (1.24 mmol/l) episodes.[6]</td><td>Electronic medical record.</td></tr>
</table>

Re-operation	An operation in the same segment as previous operation e.g. removal of material, revision due to postoperative infection, evacuation of hematoma, correction of misplaced/loose/broken implants etc.[7]	"Landspatient registeret" or the medical record via diagnostic and procedure codes (SKS-codes).
Gastrointestinal ulcer	Mucosal damage of the ventricle, lower oesophagus, duodenum or jejunum diagnosed by esophagogastroduodenoscopy procedure. Additional symptoms hereof: anaemia, hematemesis, melena, or heme-positive stool suggesting bleeding.[8]	"Landspatient registeret" or the medical record via diagnostic and procedure codes (SKS-codes).
Readmission	Any unplanned hospital admission within 90 days of discharge.[9]	"Landspatient registeret" or the medical record.

Table 4: Definition of components of the secondary outcome

	Definition	Method of recording
Pain or discomfort from the epigastrium	Pain or discomfort from the upper abdomen. A part of the dyspepsia definition[10]	Patient reported during eight-day diary: Yes/No
Reflux	Acid reflux or heartburn. A part of the dyspepsia definition [10]	Patient reported during eight-day diary: Yes/No
Diarrhoea	≥3 loose or watery stools per day.[11]	Patient reported during eight-day diary: Yes/No
Nausea	Vague, unpleasant feeling of unease with the sensation that vomiting might occur.[12]	Patient reported during eight-day diary: Yes/No
Vomiting	Forceful ejection of gastric contents from the mouth.[12]	Patient reported during eight-day diary: Yes/No
Constipation	Rome IV criteria: ≥2 of: straining, or lumpy or hard stools, or sensation of incomplete evacuation, or sensation of anorectal obstruction, or manual manoeuvres to facilitate in more than 25% of the defecations. Further, fewer than three spontaneous bowel movements per week.[13]	Patient reported during eight-day diary: Yes/No
Sedation	A state of calmness, relaxation, or sleepiness caused by certain drugs.[14]	Patient reported during eight-day diary: Yes/No
Headache	Pain in any region of the head.[15]	Patient reported during eight-day diary: Yes/No
Mood changes	Oscillation of emotional feeling tone between periods of euphoria and depression.[16]	Patient reported during eight-day diary: Yes/No
Mouth dryness	Xerostomia (subjective feeling of being dry in the mouth), often followed by symptom of thirst, dryness of lips, tenderness, stings, and burning of oral mucosa. [17]	Patient reported during eight-day diary: Yes/No

Table 5: Definition of components of the explorative outcome

	Method of recording
Pain levels	Patient reported during eight-day diary. Numeric Rating Scale (NRS) from 0-10
Analgesic treatment	Patient reported during eight-day diary
Opioid consumption	Patient reported during eight-day diary

References:

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Appendix 5

Table 6: patient ranking of the composite primary outcomes

Gender	Woman	Man	Man	Man	Man	Woman
Condition	Knee osteo-arthrosis (not scheduled for operation)	Knee osteo-arthrosis (scheduled for oxford knee)	Knee osteo-arthrosis (not scheduled for operation)	Hip osteo-arthrosis (not scheduled for operation)	Hip osteo-arthrosis (scheduled for total hip arthroplasty)	Hip osteo-arthrosis (scheduled for total hip arthroplasty)
Outcomes (1 = worst postoperative outcome, 11 = ”less worst”)						
1	Death	Death	Death	Stroke	Acute myocardial infarction	Death
2	Acute myocardial infarction	Stroke	Stroke	Acute myocardial infarction	Deep venous thrombosis	Acute myocardial infarction
3	Stroke	Acute myocardial infarction	Acute myocardial infarction	Death	Pulmonary embolism	Pulmonary embolism
4	Pulmonary embolism	Pulmonary embolism	Pulmonary embolism	Renal failure	Stroke	Deep venous thrombosis
5	Renal failure	Deep venous thrombosis	Deep venous thrombosis	Pulmonary embolism	Renal failure	Stroke
6	Deep venous thrombosis	Bleeding	Renal failure	Deep venous thrombosis	Re-operation	Bleeding
7	Bleeding	Gastrointestinal ulcer	Gastrointestinal ulcer	Re-operation	Death	Renal failure
8	Re-operation	Readmission	Readmission	Gastrointestinal ulcer	Gastrointestinal ulcer	Re-operation
9	Gastrointestinal ulcer	Renal failure	Re-operation	Bleeding	Bleeding	Gastrointestinal ulcer
10	Readmission	Re-operation	Bleeding	Readmission	Readmission	Readmission

Appendix 6

Charter for the independent Data Monitorering and Safety Committee (DMSC) of the PERISAFE trial

ClinicalTrials.gov no. NCT05575700

EU CT no. 2022-502502-32-00

Zealand University Hospital, Køge 2022

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the steering committee (SC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the steering committee of the PERISAFE trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control. The DMSC may also be asked to ensure that procedure are properly implemented to increase sample size to restore power, if protocol specified even rates are inaccurate.

The DMSC will be advisory to the steering committee. The steering committee will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC may meet physically, by phone, or online at their own discretion in order to evaluate the planned interim analyses of the PERISAFE trial. The interim analyses will be performed by the independent statistician who is part of the DMSC. The DMSC may additionally meet whenever they decide or contact each other by telephone, mail, or online in order to discuss the safety for trial participants. The sponsor has the responsibility to report the overall number of SARs yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request

unblinding of the interventions if suggested by the data, see section on 'closed sessions'. The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the steering committee of the PERISAFE trial. As fast as possible, and no later than 48 hours, the steering committee has the responsibility to inform all investigators of the trial and all the sites including patients in the trial, about the recommendation of the DMSC and the steering committee decision hereof.

If physical meetings is needed, the costs hereof will be covered by the PERISAFE trial.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of two international experts within anaesthesia and a biostatistician that, collectively, has experience in the management of orthopaedic patients and in the conduct, monitoring and analysis of randomized clinical trials.

DMSC Clinician, Trialist and biostatistician

Pending.

Conflicts of interest

DSMC members will fill in and sign a declaration of conflicts of interests. DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the PERISAFE trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organisation for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial.

The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the steering committee will appoint the replacement(s).

Formal interim analyses meeting

One formal interim analysis meeting will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DMSC will meet when 90-

day follow-up data of 1400 (approximately 50% of sample size estimation) patients have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the steering committee.

Closed reports will include analysis of the primary outcome measure. In addition, analyses of SARs will also be reported. These closed reports will be prepared by independent biostatistician being a member of the DSMC, with assistance from the trial data manager, in a manner that allow them to remain blinded.

The closed reports should provide information that is accurate, with follow-up on the primary outcome that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.

The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Steering Committee

After the interim analysis meetings, the DMSC will make a recommendation to the steering committee to continue, hold or terminate the trial.

Interim analyses will be conducted after patient no. 1400 have been followed for 90 days.

The independent DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs is found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function e.g. using the Trial Sequential Analysis software (http://ctu.dk/tsa/). If the recommendation is to stop the trial the DSMC will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all patients included at the time (including patients randomized after patient number 1400) and whether a moratorium shall take place (setting the trial at hold) in the further inclusion of patients during these extra analyses. If further analyses of the patients included after 1400 patients is recommended the rules for finally recommending stopping of the trial should obey the LanDeMets stopping boundary.

Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 33% relative risk reduction for composite outcome of 8% in the ibuprofen group will not be an option as intervention effects less than these may be clinically relevant as well.

This recommendation will be based primarily on safety considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The steering committee is jointly responsible with the DMSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the steering committee. The steering committee will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the PERISAFE trial protocol. For the two intervention groups, the DMSC will evaluate data on:

The primary outcome measure

- Composite outcome of either death, acute myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis, renal failure requiring intervention, bleeding, re-operation, gastrointestinal ulcer, or readmission within 90 days postoperatively.

The DMSC will be provided with these data from the coordinating centre as:

- Number of patients randomized
- Number of patients randomized per intervention group
- Number of patients stratified per stratification variable per intervention group
- Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

DMSC should yearly be informed about serious adverse reactions occurring in the two groups of the trial.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC

The DMSC will be provided with a file containing the data defined as follows:

Row 1 contains the names of the variables (to be defined below).

Row 2 to N (where N-1 is the number of patients having entered the trial) each contains the data of one patient.

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database:

1. screening_id: a number that uniquely identifies the patient
2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received
3. serious adverse events_comp_outc: Incidence of composite outcome 90 days postoperatively (1=one or more events, 0=no event)