Module 2.5
Clinical Expert Statement

XXX
(oral, parenteral, and topical formulations)

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Date: **Month Date, Year**

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1.1 Overview of Efficacy

Appendix I shows the results of computer-assisted investigations for publications on the subject of clinical efficacy following administration of XXX, that appeared in the period of 01/01/2014 (2006) to 01/09/2018.

Clinical Overview

General

XXX is a nonsteroidal antiinflammatory drug (NSAID) with antiinflammatory, analgesic, and antipyretic activity. Systemic XXX is effective in various pain syndromes including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, renal colic, minor surgery, trauma, and dysmenorrhea. Topical preparations are approved for resolving lesions of actinic keratosis and for the treatment of osteoarthritis of the hands and knees. Topical application has not been evaluated in patients with osteoarthritis of the spine, hip, or shoulder. XXX epolamine is a topical patch that is applied to relieve acute pain associated with minor sprains, strains, and contusions. Ophthalmic preparations are useful for controlling postsurgical inflammation following cataract removal (*Drugdex 2017*).

XXX exhibits similar efficacy to other nonsteroidal antiinflammatory drugs for treating rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, fever, and pain of various etiologies. This agent causes fewer CNS adverse effects than indomethacin and less gastrointestinal irritation than aspirin or indomethacin. XXX is structurally unique compared to the other NSAIDs (*Drugdex 2017*). At doses commonly used in rheumatoid arthritis, XXX significantly inhibits both cyclo-oxygenase-1 and cyclo-oxygenase-2, whereas etoricoxib and celecoxib significantly inhibit cyclo-oxygenase-2 and do not substantially inhibit cyclo-oxygenase-1. Prostaglandin E2 synthesis was inhibited with a rank order of potency of XXX > etoricoxib > celecoxib (XXX *et al. 2013*).

All NSAIDs are considered therapeutically equivalent although their antiinflammatory, antipyretic, and analgesic properties vary to a small degree. In general, the NSAIDs share similar adverse reactions, although the frequency and severity may vary among specific agents. The distinguishing factors between the NSAIDs include pharmacokinetic properties, specific pharmacological action, and clinical characteristics. Each patient being treated with NSAIDs is unique, thus for the most appropriate therapy to be achieved practitioners should base the agent selection on the adverse reaction profile, concurrent therapy, simplicity of dosage regimen, patient compliance, and overall cost of treatment (*Drugdex 2017*).

In addition to its potent antiinflammatory activity, XXX was found to possess antibacterial activity against both drug-sensitive and drug-resistant clinical isolates of *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli*, and *Mycobacterium spp*. The time-kill curve study indicates that this nonsteroidal drug exhibits bactericidal activity against *Listeria*, *Escherichia coli*, and *Mycobacterium tuberculosis*. The antibacterial activity of XXX comes, in part, from its ability to inhibit the DNA synthesis of *Escherichia coli* and *Listeria monocytogenes*. XXX could protect murine listeriosis, salmonellosis, and tuberculosis at doses ranged within its maximum recommended human or non-toxic ex-vivo dose. XXX possesses anti-plasmid activity and acts as a 'helper compound' in synergistic combination with streptomycin against *Escherichia coli* and *Mycobacterium* or gentamicin against *Listeria* (XXX *et al. 2016*).

Osteoarthritis

XXX is a commonly used nonsteroidal antiinflammatory drug for symptom control in osteoarthritis of the knee and soft tissue injuries. In the majority of studies examined, topical XXX formulations with lotion, lecithin or epolamine gel, patch or plaster were either superior or equivalent to oral XXX formulations or placebo. Topical XXX significantly reduced pain and morning stiffness and improved physical function and patient global assessment without major adverse effects reported in patients with osteoarthritis of the knee, and provided significant pain relief in patients with sports and soft tissue injuries involving the ankle, knee or shoulder (*XXX 2013*). XXX gel decreased pain intensity scores by 42%-45%, total Australian/Canadian Osteoarthritis Hand Index scores by 35%-40%, and global rating of disease by 36%-40% (*XXX et al. 2016*). Over a 3-month treatment period, topical treatment with XXX gel (1%) achieved statistically and clinically significant improvements of pain and measures of physical function in patients with knee osteoarthritis (*XXX et al. 2016*).

The efficacy and safety of oral XXX (100-150 mg/day) as early treatment of acute sciatica/lumbo-sciatica was similar to lornoxicam (8-24 mg/day) in a 5-day double-blind, randomised study in (XXX *and* XXX *2016*). Interestingly, the combination of XXX with B vitamins was significantly superior to XXX monotherapy in lumbago relief after 3 days of treatment (XXX *et al. 2016*). Compared to occlusal splint therapy, XXX (50 mg three times daily) gave a more rapid improvement, but both treatments gave a significant reduction of symptoms of temporomandibular joint osteoarthritis (n=29 patients) within 3 months which remained at the one-year follow-up (XXX *and* XXX *2013*).

Topical XXX 1% gel treatment (4 g four times daily) provided effective pain relief and functional improvement of osteoarthritis in one or both knees in a double-blind, placebo-controlled study. At week 12, XXX (n=208) provided significantly greater reductions in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (52.6% vs. 43.1%; p=0.008) and physical function (49.7% vs. 39.4%; p=0.004) versus vehicle (n=212) and provided significant improvements in most secondary endpoints. Treatment-related adverse events were infrequent (7.7% vs. 4.2%), with application site dermatitis being the most common (4.8% vs. 0%). No treatment-related gastrointestinal or serious adverse events occurred with XXX 1% gel (*XXX et al. 2012*).

Pooled data from three double-blind, parallel-group, placebo-controlled trials conducted in elderly (n=374) and younger (n=602) patients with knee osteoarthritis showed topical XXX (1% gel, 4 g four times daily on one knee for 12 weeks) effective and generally well tolerated in adults regardless of age. Among patients aged 25-64 years, the improvement from baseline to week 12 was greater for XXX versus vehicle for WOMAC pain (-5.8 vs. -4.7; p=0.007), WOMAC physical function (-17.9 vs. -14.2; p=0.002), global rating of disease (-29.5 vs. -23.8; p=0.01) and pain on movement (-37.3 vs. -29.0; p<0.001). Among patients aged ≥ 65 years, the improvements from baseline were for WOMAC pain (-5.3 vs. -4.1; p=0.02), WOMAC physical function (-15.5 vs. -11.0; p=0.004) and pain on movement (-33.7 vs. -26.4; p=0.02) (*XXX et al. 2015*). In elderly patients (≥ 65 years) with osteoarthritis or rheumatic arthritis participating the CONDOR trial, the efficacy of treatment was comparable in the groups using celecoxib (200 mg twice daily) (n=1219) and slow release XXX (75 mg daily) plus omeprazole (n=1227). There were fewer endpoints as well as fewer gastrointestinal adverse events (p<0.001) reported in patients treated with celecoxib compared with XXX (XXX *et al. 2017*). According to a recent review of 37 controlled trials that compared XXX with other pain relief medications in osteoarthritis, the efficacy of XXX is largely unchallenged in that it remains as effective as newer pain relief medications employed in osteoarthritis (XXX *2017*).

Rheumatoid Arthritis

In the treatment of patients with rheumatoid arthritis (n=4086) etoricoxib (90 mg daily) and XXX (75 mg twice daily) resulted in similar efficacy in a double-blind controlled study. Etoricoxib demonstrated a significantly lower risk for discontinuing treatment due to gastrointestinal adverse events compared with XXX ($p \leq 0.001$) (XXX *et al. 2013*).

Ankylosing Spondylitis

Comparable analgetic efficacy of XXX (75 mg twice daily) and celecoxib (200 mg once and twice daily) was demonstrated in a 12-week double-blind controlled study (n=458). Ankylosing Spondylitis Assessment Study group 20% response and mean improvement in Bath Ankylosing Spondylitis Disease Activity Index scores at week 12 were numerically better on twice-daily celecoxib (59.7% and -1.32 points) and on XXX (60.2% and -1.48 points) than on once-daily celecoxib (46.0% and -0.99 points). The incidence of gastrointestinal adverse events was significantly higher on XXX (28.4%) than on celecoxib (15.0% to 16.7%) (XXX *et al. 2013*).

Actinic Keratosis

In the past decade, numerous clinical studies (17) have demonstrated topical therapy with 3% XXX gel to be effective and well tolerated for the treatment of actinic keratosis. An open-label study reported 58% complete clearance of target lesions at day 30 post-treatment. Among patients who were evaluable at 1-year post-treatment, sustained long-term clearance of lesions was observed. Active comparator studies demonstrated comparable efficacy of XXX 3% gel with 5-fluorouracil 5% and imiquimod 5%. Publications on the efficacy of XXX 3% gel for actinic keratosis of the lip report complete clearance rates comparable to those reported for other body areas. XXX 3% gel has also demonstrated efficacy for clearing actinic keratosis lesions in immunosuppressed populations (XXX *and* XXX *2017*). A case series (n=4) showed the successful use of topical 3% XXX gel for the management of periocular actinic keratosis. In all the patients, a visible decrease in lesion severity was seen after 1 month, and complete resolution, within 4 months. Recurrences occurred in 2 patients at 4 months and 7 months after treatment. An adverse reaction in 1 patient resolved with discontinuation of XXX (*XXX et al. 2017*). Results of an open-label study in six patients (three kidney, one liver and two heart transplant patients) with histories of multiple non-melanoma skin cancers and extensive actinic keratoses suggest that XXX 3% gel may be useful in the treatment and control of multiple actinic keratosis lesions in organ transplant recipients (XXX *et al. 2014a*). A placebo-controlled study of topical XXX 3% gel (twice daily for 16 weeks) in organ transplant patients with multiple actinic keratoses (n=32) demonstrated a complete clearance of actinic keratosis lesions in 41% (9/22) in the XXX group compared to 0% (0/6) in the vehicle group. Side effects in most of the patients included a mild erythema and mild to moderate swelling of the areas treated. No graft rejections or trends for a deterioration of graft function were detected. No meaningful trends were observed in laboratory results. In 55% of the previously cleared patients new actinic keratoses developed in the study area after an average of 9.3 months. None of these patients developed invasive squamous cell carcinomas within 24 months of follow-up (XXX *et al. 2012*). The sequential treatment with cryosurgery followed by XXX 3% gel for 90 days is well tolerated and can provide a therapeutic modality that may provide patients with actinic keratoses a more successful outcome than monotherapy with cryosurgery by effectively treating clinical and subclinical lesions (*XXX 2013*).

Cheilitis

Actinic cheilitis is a frequent manifestation of actinic dysplasia and requires early therapy to prevent its progression into invasive squamous cell carcinoma. Several therapies are used, ranging from unspecific lesion-adapted destructive techniques (i.e. laser) to ambitious

surgical field-management (vermillionectomy). There is increasing awareness of the effectiveness of field adapted, non-destructive therapies, such as photodynamic therapy or 5% imiquimod. XXX (3% gel) is used in the treatment of actinic keratosis, but it has not been evaluated for the treatment of actinic cheilitis. Topical therapy with XXX 3% gel may be an efficient, cosmetically more appealing alternative treatment for actinic cheilitis than currently used destructive therapies. However, future studies and long-term follow-up of patients will be needed to compare its efficacy with established forms of therapy (XXX *et al. 2014b*).

Acute Menstrual Pain

Rofecoxib (25 mg) and XXX (50 mg) were equally effective in alleviating pain associated with primary dysmenorrhea (n=11). Both decreased the duration of dysmenorrheic pain compared with placebo ($p<0.001$) and with meloxicam ($p<0.01$), and were equally effective in analgesia, compared with placebo, after each capsule ($p<0.001$). When compared with placebo, both drugs also provided ≥ 50% pain relief, after each capsule ($p<0.0048$) (XXX *et al. 2013*). XXX potassium (100 mg daily) is effective in relieving menstrual pain and restoring physical performance to levels achieved when the women were in the late-follicular (no menstruation, no pain) phase of the menstrual cycle (XXX *et al. 2016*). Administration of XXX potassium (150 mg daily) compared to placebo not only attenuated the women's menstrual pain ($p<0.05$), but also increased sleep efficiency ($p<0.05$) and percentage of REM sleep ($p<0.01$), decreased percentage of stage 1 sleep ($p<0.05$) and number of sleep stage changes per hour of sleep ($p<0.05$), and improved subjective ratings of sleep quality and morning vigilance ($p<0.05$) (XXX *et al. 2016*).

Headache

According to a review of 5 studies (n=1356), oral XXX potassium 50 mg is an effective treatment for acute migraine, providing relief from pain and associated symptoms, although only a minority of patients experienced pain-free responses. For single doses of XXX versus placebo (two studies), the number needed to treat to benefit were 6.2, 8.9, and 9.5 for pain-free at 2 hours, headache relief at 2 hours, and pain-free response at 24 hours, respectively. Associated symptoms of nausea, photophobia and phonophobia, and functional disability were reduced within 2 hours, and similar numbers of participants experienced adverse events (XXX *et al. 2017*).

Inflammatory Pain

An evidence-based review (on several published double-blind, placebo-controlled trials) shows topical XXX to be an effective and well tolerated treatment in painful and inflammatory conditions, at least in the short-term. Future trials of topical XXX need to be of longer duration, be better reported and consider a broader spectrum of acute and chronic pain indications (XXX *et al 2013*). XXX (75 mg twice daily for 10 days) and paracetamol (500 mg three times daily) had the same effect on pain reduction of ankle sprains but more acute ankle edema was present in patients who were treated with XXX (n=45) than in patients who were treated with paracetamol (n=45). By the 10^{th} post-traumatic day no difference was found. Pain decreased in both groups at the third day and at the tenth day ($p<0.001$) (XXX *et al. 2015*).

Pain Reduction during Panretinal Laser Photocoagulation

When given in a single dose, oral XXX is an effective pretreatment analgesic agent for reducing the pain experienced during panretinal laser photocoagulation for proliferative diabetic retinopathy (XXX *et al. 2016*).

Postoperative Pain

Based on systematic reviews of 15 studies (8 additional studies) with 1512 participants, oral XXX (50 mg and 100 mg) is an effective single-dose treatment for moderate to severe

postoperative pain. Significantly more participants experienced at least 50% pain relief over 4 to 6 hours with XXX potassium than with XXX (XXX *et al. 2016*).

Comparison of XXX (100 mg) (n=35) with indomethacin (100 mg) suppositories (n=35) for mediolateral episiotomies showed that both provided analgesia (p<0.05), however, XXX was more effective (*XXX et al. 2017*). The prophylactic use of XXX suppositories reduced perineal pain more than the use of indomethacin suppositories, although the difference was not significant. Overall additional analgesia requirement was correspondingly lower in the XXX group (XXX *et al. 2016*). Rectal XXX in combination with caudal block provides good, post-operative analgesia in early as well as in later post-operative period in comparison to caudal block alone which provides analgesia only in early post-operative period (XXX *et al. 2013*).

A double-blind, placebo-controlled study in patients undergoing laparoscopic cholecystectomy (n=80) demonstrated that the preemptive administration of a combination of low-dose ketamine plus XXX improved postoperative analgesia. Patients receiving XXX had a significantly lower pain score between 2 and 6 hours after surgery compared with patients receiving placebo. One hour after surgery, patients receiving a combination of XXX and ketamine had a significantly lower pain score compared with placebo and ketamine alone. Patients from all the 4 study groups required postoperative analgesic; however, the time to XXX request was longer in patients receiving a combination of XXX and ketamine compared with patients receiving placebo (p<0.001), ketamine (p<0.001), or XXX (p=0.03) alone (XXX *et al. 2017*).

In patients undergoing prostatectomy (n=96) under general anesthesia wound infiltration with bupivacaine during surgical closure combined with XXX (75 mg intramuscular) administration reduced postoperative tramadol consumption more than bupivacaine alone (p<0.05) in a double-blind, placebo-controlled study (*XXX et al. 2015*). Preoperative XXX (75 mg intramuscularly) and (tramadol (50 mg intramuscularly) in patients who underwent bimaxillary osteotomy (n=36) similarly reduced postoperative pain intensity and postoperative opioid consumption with intravenous patient-controlled analgesia (XXX *et al. 2014*).

A double-blind study compared the analgesic effects of dexketoprofen (50 mg intramuscularly) and XXX (75 mg intramuscularly) during shockwave lithotripsy. The mean visual analog scale score for dexketoprofen was statistically lower compared with the score for XXX (p=0.02). The procedure was performed with no, minor, or tolerable pain in 85% (34/40) of patients in the XXX group versus 93.3% (28/80) patients in the dexketoprofen group (p=0.01). No major/minor adverse effects were observed in XXX patients, whereas in one dexketoprofen patient, dyspepsia after injection was noticed (p=0.423) (XXX *et al. 2012*). A novel formulation of injectable XXX is solubilized with hydroxypropyl beta-cyclodextrin (HPbetaCD) so that it can be given intravenous or intramuscular in a small volume bolus. For patients with acute moderate and severe pain after abdominal or pelvic surgery (n=331), repeated 18.75 mg and 37.5 mg doses of HPbetaCD XXX provided significant analgesic efficacy and reduced the needs for opioids, as compared to placebo in a double-blind-controlled study (XXX *et al. 2017*). In a single dose, double-blind, placebo- and comparator-controlled parallel group study subjects with postoperative third molar extraction pain (n=353) received placebo, ketorolac (30 mg) or intravenous XXX (3.75, 9.4, 18.75, 37.5, or 75 mg). XXX (both, 37.5 mg and 75 mg) was superior to placebo (p<0.05) at the earliest (5 minute) assessments of pain intensity and pain relief, but ketorolac was not. The proportion of patients reporting ≥ 30% pain relief at 5 minutes was significantly greater after XXX than after ketorolac or placebo (XXX *et al. 2015*).

Rectal XXX suppository (100 mg) with tramadol provides adequate pain relief after cardiac surgery, and also reduces tramadol consumption and side effects commonly associated with tramadol (XXX *et al. 2016*). Placebo-controlled, parallel-group studies have demonstrated a

significant opioid sparing effect after abdominal hysterectomy with preoperative XXX, but not with meloxicam (*XXX et al. 2013*). XXX alone was safe and effective for the majority of the patients undergoing cesarean section and it decreased the opioid requirements in the remaining patients. Patients (n=130) receiving XXX alone (75 mg twice daily) or a combination of XXX (75 mg twice daily) and meperidine (50 mg twice daily) were less sedated and the time to the first passing of flatus was shorter than that in the patients treated with only meperidine (XXX *et al. 2016*).

XXX transdermal patch provided pain relief for postoperative laparoscopic surgery as effectively as intramuscular XXX (75 mg 15 min before anesthesia) (XXX *et al. 2017).*

Postoperative Analgesia in Children

According to a meta-analysis, XXX is also an effective analgesic for perioperative acute pain in children (XXX *et al. 2016*). In a placebo-controlled study in children (n=12) rectal acetaminophen (40 mg/kg bodyweight) plus XXX (1 mg/kg bodyweight) was found to be the most effective in pain control. However, both rectal acetaminophen and XXX alone were more effective than placebo, whereas XXX was more effective than acetaminophen (XXX *and* XXX *2015*).

Hip Arthroplasty/Arthroscopy

A parallel-group, double-blind controlled study comparing celecoxib (200 mg four times daily) and XXX (50 mg three times daily) in patients with osteoarthritis of the hip requiring joint replacement (n=249) showed improvement of arthritis pain on walking in both groups. However, treatment differences in change from baseline favored XXX at week 6 and week 12. A post hoc analysis, performed after unblinding due to an imbalance in the numbers of patients previously receiving NSAIDs, found a greater treatment difference at week 6 between celecoxib and XXX in arthritis pain, favoring XXX, in previous nonusers of NSAIDs (n=49) compared with previous NSAID users (n=92). A similar proportion of patients in celecoxib and XXX groups experienced adverse events (53.6% vs. 53.7%) (XXX *et al. 2013*).

Cesarien Delivery

Postoperative analgesia produced by local XXX infusion was as effective as local ropivacaine infusion with systemic XXX in cesasien delivery (XXX *et al. 2014*).

Conception Cycles

Insufficient information is available on the efficacy and safety of the potent analgesic XXX administered following oocyte retrieval. On basis of a double-blind study of assisted conception cycles (n=381), the use of XXX did not significantly compromise the implantation and pregnancy rates. Patients randomized to receive XXX had statistically significantly reduced pain scores prior to discharge (p=0.030) (XXX *et al. 2013*).

Laparoscopic Sterilization

Preoperative rectal XXX (100 mg) and intravenous parecoxib (40 mg) at induction of anesthesia were found to have equianalgesic effects after laparoscopic sterilization. Both drugs appear to be useful after short anesthetics (XXX *et al. 2013*).

Cataract Surgery

Visual acuity in XXX (postoperatively, topical XXX was applied 4 times daily for 1 eye) eyes significantly improved following the cataract surgery. Foveal thickness in both eyes gradually increased at week 4 and week 8 after the cataract surgery. Intraocular pressure in XXX-treated eyes decreased with time throughout the observational period (XXX *et al. 2014*). Preservative-free XXX 0.1% eyedrops exhibited a significantly better postoperative

tolerability when compared with preserved eyedrops containing ketorolac or XXX. All 3 formulations demonstrated equal anti-inflammatory efficacy as measured by reduction of anterior chamber flare after surgery and prevention of postoperative macular edema. Patients treated with preservative-free XXX eyedrops reported better subjective tolerability values (p=0.001), were classified as having less ocular discomfort (p<0.001), and experienced earlier reduction of postoperative conjunctival hyperemia (p=0.029) (XXX *et al. 2012*).

Tonsillectomy

Sequential clot strength analyses following XXX in pediatric adenotonsillectomy (n=20) suggest that preoperative XXX does not adversely affect clot strength in the immediate postoperative period when the risk of primary hemorrhage is greatest (XXX *et al. 2014*).

Endoscopic Retrograde Cholangiopancreatography/Acute Pancreatitis

A recent double-blind controlled trial in patients (n=100) confirms above mentioned results. In this regard, rectal XXX given immediately after endoscopic retrograde cholangiopancreatography can reduce the incidence of acute pancreatitis (XXX *et al. 2013*). Intramuscular XXX (at a loading dose of 75 mg) and fluid replacement lowered the rate of pancreatitis in patients without sphincter of Oddi dysfunction (XXX *et al. 2016*).

Nocturnal Polyuria

A double-blind, crossover study showed a significant improvement of symptoms in patients with nocturnal polyuria (n=26) and treated with XXX (50 mg daily for 2 weeks) when compared with placebo. The mean nocturnal frequency decreased from 2.7 to 2.3 (p<0.004) and the mean ratio of night-time to 24 hour urine volume decreased from 44% to 39% (p<0.001). No significant side effects were reported (*XXX et al. 2006*).

Analgesia after Conventional Radio Frequency Neurotomy

A double-blind placebo-controlled trial showed efficacy of XXX in pain relief after conventional radiofrequency denervation for chronic facet joint pain (n=66). Compared to a 7-day dosage, a 3-day XXX therapy had similar efficacy. Visul analog score in 3- and 7-day groups both was less than that in placebo group at 1 and 7 days after treatment (p<0.05 and 0.01, respectively). Patients' Satisfaction Score in XXX groups was significantly better than in placebo group at 30 and 60 days after treatment (p<0.05). The rate of side effects was similar among the three groups at all times (p>0.05) (XXX *et al. 2015*).

Analgesia after Hernia Repair Surgery

Midazolam (0.05 mg/kg bodyweight) enhanced the postoperative analgesic effects of XXX (1.5 mg/kg bodyweight) when used (15 minutes) before surgical incision in patients scheduled for hernia repair surgery (n=90). a significantly lower proportion of patients exhibited postoperative pain than in XXX only group (11.1% vs. 37.7%, respectively; p<0.05). The Verbal Rating Scale-6 score was 1.4 vs. 2.4, respectively. Mean Observer's Assessment of Alertness/Sedation score in the midazolam+XXX group was lower than in the XXX group (1.5 vs. 3.3, respectively; p<0.05). Duration of sedation was 22.5 min vs. 12.1 min, respectively (p<0.01). The first postoperative analgesic request after surgery was 120 min vs. 60 min, respectively (p<0.05) (XXX *et al. 2012*).

Postoperative Dental Pain

In a double-blind, placebo-controlled trial of XXX potassium liquid-filled soft gelatin capsule (DPSGC) for treatment of postoperative dental pain, a total of 249 patients after third molar extraction had a significant increase in the summed pain intensity difference and total pain relief values at 3 and 6 hours across all XXX groups (single dose 25, 50, or 100 mg) compared with the placebo group (p<0.0001). The onset of perceptible and meaningful pain

relief was significantly faster in all DPSGC groups than in the placebo group, including the DPSGC 25-mg group (25 minutes [p=0.0002] and 52 minutes [p<0.0001] for perceptible and meaningful pain relief, respectively). Significantly fewer patients in the DPSGC groups required rescue medication compared with those in the placebo group (p<0.0001). The global evaluation scores were significantly greater for the patients who received DPSGC than for those who received placebo (p<0.0001), and more than 65% of DPSGC-treated patients rated the medication as good, very good, or excellent compared with 18% of the placebo-treated patients (XXX *et al. 2012*). A XXX containing preparation appears to be the better pre-emptive analgesic for dental extractions under general anesthesia when compared with paracetamol and no analgesia (XXX *et al. 2014*). A double-blind, placebo-controlled study data suggest that lower dose nano-formulated oral XXX (35 mg) could be effective for acute pain following third molar extraction (n=232) and may potentially improve safety and tolerability as a result of using a lower overall dose (XXX *et al. 2017*).

Microneedle Treatment

XXX delays micropore closure following microneedle treatment in human subjects. Area under the admittance-time curve was significantly higher at microneedle plus XXX sites versus placebo, suggesting slower rates of micropore healing (*Brogden et al. 2017*).

1.2 Summary of Efficacy

Literature derived basic scientific data show the therapeutic effectiveness from clinical use of XXX in various clinical pain conditions (see *Appendix I*).

XXX possess antiinflammatory, antipyretic, and analgesic properties. XXX systemic is effective in various pain syndromes including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, renal/biliary colic, minor surgery, trauma, and dysmenorrhea. Ophthalmic preparations are useful for controlling postsurgical inflammation following cataract removal (*Drugdex 2017*). Effectiveness of XXX has been confirmed repeatedly and appears similar to colecoxib (XXX *et al. 2017*) and various other comparator pain relieving drugs (XXX *2017*). Interestingly, XXX was found to possess antibacterial activity against both drug-sensitive and drug-resistant clinical isolates of *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli*, and *Mycobacterium spp*., in addition to its potent anti-inflammatory activity (XXX *et al. 2016*).

Oral XXX (50 mg and 100 mg) is an effective single-dose treatment for moderate to severe postoperative pain. Significantly more participants experienced at least 50% pain relief over 4 to 6 hours with XXX potassium than with XXX (XXX *et al. 2016*). XXX is also an effective analgesic for perioperative and postoperative acute pain in children (XXX *et al. 2016,* XXX *and* XXX *2015*) and lower dose nano-formulated oral XXX (35 mg) for postoperative pain following third molar extraction (XXX *et al. 2017*).

Efficacy of oral and topical XXX has been shown in painful and inflammatory conditions (XXX *et al 2013*), mostly in osteoarthritis of the hips and/or knees (XXX *and* XXX *2016*, *XXX 2013, XXX et al. 2013*, *XXX et al. 2016*). In patients with rheumatoid arthritis, hip osteoarthritis or ankylosing spondylitis comparable analgesic effectiveness has been demonstrated for etoricoxib (XXX *et al. 2013*) or celecoxib and oral XXX *(*XXX *et al. 2013,* XXX *et al. 2013*). Recent data indicate that the analgesic efficacy of XXX is superior to placebo and similar to lornoxicam in acute sciatica/lumbo-sciatica (XXX *and* XXX *2016*). Topical XXX (1% gel) was effective in adults with knee osteoarthritis regardless of age (*XXX et al. 2015*, *XXX et al. 2012*). In the treatment of ankle sprains XXX and paracetamol have been shown similar efficacy (XXX *et al. 2015*).

Randomised, double-blind trials with both placebo and active controls have demonstrated the efficacy of XXX potassium (12.5 mg tablets) in conditions suitable for treatment with OTC medication, for example, acute lower back pain, headache, acute pain after dental extraction, symptoms of cold and influenza (including fever), and pain from dysmenorrhea (XXX *2014*, XXX *et al. 2013,* XXX *et al. 2016*). XXX potassium effectively attenuates nighttime dysmenorrheic pain and restores subjective and objective measures of sleep quality to values recorded in a pain-free phase of the menstrual cycle (XXX *et al. 2016*).

Topical preparations are approved for resolving lesions of actinic keratosis (*XXX 2013*) or cheilitis (XXX *et al. 2014b*). Topical therapy with 3% XXX gel has been repeatedly shown be effective and well tolerated for the treatment of actinic keratosis (XXX *and* XXX *2017*, *XXX et al. 2017*). XXX 3% gel may be useful in the control of multiple actinic keratosis lesions in organ transplant recipients (XXX *et al. 2014a*). Results of a small placebo-controlled study demonstrate efficacy of topical XXX 3% gel in organ transplant patients with multiple actinic keratoses and suggest that the treatment also may prevent invasive squamous cell carcinomas (XXX *et al. 2012*).

Literature derived basic scientific data show the therapeutic effectiveness from clinical use of XXX in post-operative pain and inflammation (after knee arthroplasty/arthroscopy, cataract surgery, varicose vein surgery, cesarean section, tonsillectomy, extraction of molars, corneal abrasions, inguinal hernia repair, laparoscopic sterilization) (XXX *et al. 2013,* XXX *et al.*

2014, XXX *et al. 2014*, XXX *et al. 2012*, XXX *et al. 2016*, XXX *et al. 2016*). An opioid sparing effect was demonstrated with the preoperative use of XXX after abdominal hysterectomy (*XXX et al. 2013*), after bimaxillary osteotomy (XXX *et al. 2014*), and cesarean section (XXX *et al. 2014*, XXX *et al. 2016*). Intramuscular XXX reduced postoperative tramadol consumption in patients undergoing prostatectomy (*XXX et al. 2015*). The preemptive administration of a combination of low-dose ketamine plus XXX improved postoperative analgesia after laparoscopic cholecystectomy in a double-blind, placebo and mono-therapy-controlled study (XXX - XXX *et al. 2017*).

Dyloject, a novel formulation of intravenous XXX has provided superior postoperative analgesia as compared to ketorolac and placebo (XXX *et al. 2015*, XXX *et al. 2017*).

Rectal XXX has been found to be safe and effective adjunct to sufficient post-operative analgesia (XXX *et al. 2013*) and was superior to indomethacin after mediolateral episiotomy (*XXX et al. 2017*). Transdermal XXX has been shown as effective as intramuscular XXX for postlaparoscopic analgesia (XXX *et al. 2017).*

Postoperative macular thickening following cataract surgery in patients with non- or mild nonproliferative-diabetic retinopathy cannot be fully suppressed by topical XXX. Nonetheless, XXX protected against an early event of postoperative cystoid macular edema and also a decrease of intraocular pressure (XXX *et al. 2014*). Preservative-free XXX 0.1% eyedrops exhibited a significantly better postoperative subjective and objective tolerability when compared with preserved eyedrops containing ketorolac or XXX (XXX *et al. 2012*). When given in a single dose, oral XXX is an effective pretreatment analgesic agent for reducing the pain experienced during panretinal laser photocoagulation for proliferative diabetic retinopathy (XXX *et al. 2016*).

Moreover, the incidence of acute pancreatitis can be reduced by rectal (XXX *et al. 2013*) or intramuscular (XXX *et al. 2016*) XXX given immediately after endoscopic retrograde cholangiopancreatography (XXX *et al. 2013*).

XXX improved analgesia and the Patients' Satisfaction Score after radio frequency denervation (XXX *et al. 2015*). During shockwave lithotripsy analgesia appeared more effective with dexketoprofen than with XXX (XXX *et al. 2012*).

Midazolam enhanced the postoperative analgesic effects of XXX when used before the onset of noxious stimuli (XXX *et al. 2012*).

Beyond it, good therapeutic effects have also been demonstrated in the treatment of nocturnal polyuria (*XXX et al. 2006*).

Administration of XXX for analgesia following oocyte retrieval had statistically significantly reduced pain scores prior to discharge, but did not compromise treatment outcome (XXX *et al. 2013*).

XXX delayed micropore closure following microneedle treatment (*Brogden et al. 2017*).

2 Clinical Safety

2.1 Overview of Safety

Appendix I shows the results of computer-assisted investigations for publications on the subject of adverse drug reactions and drug interactions following administration of XXX, that appeared in the period of 01/01/2014 (2006) to 01/09/2018.

Adverse Drug Reactions

General

Cardiovascular Effects

Fluid retention and edema have been reported in 1% to 3% of patients receiving XXX. hypertension and congestive heart failure occurred in less than 1% of patients taking XXX. Use of nonsteroidal anti-inflammatory agents (NSAIDs), including XXX, may increase the risk of myocardial infarction (incidence: < 2%). Thrombotic events have been reported during therapy with nonsteroidal anti-inflammatory agents, including XXX. The risk of thrombotic events may increase with increased duration of use (*Drugdex 2017*).

Dermatologic Effects

Rash and pruritus have been reported in 1% to 3% of patients during treatment with XXX. alopecia, urticaria, eczema, and dermatitis have been reported in less than 1% of patients (*Drugdex 2017*).

Endocrine/Metabolic Effects

XXX enhances the actions of antidiuretic hormone due to prostaglandin inhibition. This is counterbalanced by the release of vasopressin from the CNS, resulting in no net change in water balance in most patients. Water intoxication and hyponatremia only occur with NSAIDs in clinical practice in patients in a state of endogenous or exogenous active antidiuretic hormone secretion, such as in elderly or neonatal patients, chronic renal failure, low salt diet, excessive oral water intake, heart failure, or concurrent analgesic use. Patients with acute, intermittent porphyria possess a defect in the regulation of (delta-amino levulinic acid) ALA-synthetase which is responsible for increasing the production of porphyrins. A number of drugs, including XXX, stimulate enzymes, including the formation of ALA-synthetase. This may cause a precipitous and dangerous rise in the level of porphyrins (*Drugdex 2017*).

Gastrointestinal Effects

The most common adverse effects associated with XXX are gastrointestinal and may occur in up to 20% of patients. Gastrointestinal adverse effects include diarrhea (3-9%), indigestion (3-9%), nausea (3-9%), constipation (3-9%), and flatulence (1-3%), ulcerations, bleeding, or perforation (1-3%) (*Drugdex 2017*).

Hematologic Effects

Anemia has been reported during therapy with nonsteroidal anti-inflammatory agents, including XXX. Acute immune hemolytic anemia has been reported more frequently over time. Onset of intravascular hemolysis has ranged from 1 week to 2 years after the initiation of XXX therapy. Inhibition of platelet aggregation and prolongation of bleeding time has been reported with the administration of XXX (*Drugdex 2017*).

Hepatic Effects

Rare cases of jaundice, hepatic failure, hepatic necrosis, and hepatitis have been reported during treatment with nonsteroidal anti-inflammatory agents, including XXX (*Drugdex 2017*).

Immunologic Effects

XXX should not be given to patients with the aspirin triad, a symptom complex including asthma, rhinitis with or without nasal polyps, and sensitivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, sometimes fatal, anaphylactoid reactions to NSAIDs have been reported in these patients. Anaphylactoid reactions have been reported in patients with no known history of prior exposure to nonsteroidal anti-inflammatory drugs (*Drugdex 2017*).

Neurologic Effects
Central nervous system side effects are the second most frequent adverse reactions associated with XXX therapy. headache has been reported in 7% of XXX-treated patients and dizziness in 3%. vertigo, insomnia, drowsiness, agitation, depression, irritability, and anxiety have been reported in less than 1% of patients who received XXX during clinical trials or after it was marketed. Use of nonsteroidal anti-inflammatory agents (NSAIDs), including XXX, may increase the risk of stroke. The risk appears to increase with increased duration of NSAID use. Pre-existing cardiovascular disease or risk factors for cardiovascular disease also increase the risk of stroke (*Drugdex 2017*).

Otic Effects
Tinnitus has been reported in 1% to 3% of patients treated with XXX during clinical trials (*Drugdex 2017*).

Renal Effects
XXX may precipitate acute renal failure in patients, who are dependent on renal prostaglandins for maintenance of renal blood flow (*Drugdex 2017*).

Respiratory Effects
Severe bronchospasm (incidence: < 2%) has been reported in patients with aspirin-sensitive asthma. Cross-reactivity between aspirin and other non-steroidal anti-inflammatory agents has been reported in aspirin-sensitive patients (*Drugdex 2017*).

ADR Reports
Summary of Listed Adverse Drug Reactions (ADRs)
The commonest adverse effects of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhea. These are usually mild and reversible but in some patients peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that inhibition of cyclo-oxygenase-1 (COX-1) plays an important role in the gastrointestinal effects of NSAIDs; the selective inhibition of COX-2 improves gastrointestinal tolerance. CNS-related adverse effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Some patients may experience visual disturbances. Hematological adverse effects of NSAIDs include anemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Unlike aspirin, inhibition of platelet aggregation is reversible with other NSAIDs. Some NSAIDs have been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Hematuria has also occurred. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy. Fluid retention may occur, rarely precipitating heart failure in susceptible patients. Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis has also been reported. There may be pain and, occasionally, tissue damage at the site of injection when XXX is given intramuscularly. XXX suppositories can cause local irritation. Transient burning and stinging

may occur with XXX ophthalmic solution; more serious corneal adverse effects have also occurred. Topical preparations of XXX, such as plasters and gel, may cause application site reactions (see *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97]* from 30/09/2017 [Data Lock Point]).

Detailed Unlisted Adverse Drug Reactions (ADRs)
According to the line-listing table of serious unlisted symptoms from spontaneous, regulatory, and literature source (time period: 01/90/2016–30/09/2017), adverse drug reactions like **Blood/Lymphatic system disorders** (Anaemia, Anaemia haemolytic autoimmune, Coagulopathy, Disseminated intravascular coagulation, Haemolysis, Haemolytic uraemic syndrome, Haemorrhagic anaemia, Leukocytosis, Microcytic anaemia, Neutropenia, Spleen disorder), **Cardiac disorders** (Arrhythmia, Arteriosclerosis coronary artery, Atrial fibrillation, Bradycardia, Cardiac arrest, Cardiac disorder, Cardio-respiratory arrest, Cardio-respiratory distress, Coronary artery disease, Cyanosis, Kounis syndrome, Palpitations, Pericarditis, Tachycardia, Tachycardia paroxysmal), **Congenital/Familial/Genetic disorders** (Aplasia cutis congenita, Factor V deficiency, Factor VIII deficiency, Porphyria acute, Porphyria non-acute), **Eye disorders** (Abnormal sensation in eye, Conjunctival haemorrhage, Conjunctival oedema, Conjunctivitis, Eye pain, Eye swelling, Lacrimation increased, Ocular hypertension, Retinopathy hypertensive), **Gastrointestinal disorders** (Abdominal hernia, Abdominal pain, Abdominal rigidity, Ascites, Barrett's oesophagus, Colitis ischaemic, Colitis microscopic, Dental caries, Diaphragmatic hernia, Diarrhoea, Diverticular perforation, Duodenitis, Enteritis, Erosive oesophagitis, Faeces discoloured, Gastrointestinal disorder, Gastrointestinal tract mucosal pigmentation, Gastrooesophageal reflux disease, Hiatus hernia, Mallory-Weiss syndrome, Oedematous pancreatitis, Oesophageal ulcer, Oral discomfort, Oral pain, Palatal oedema, Pancreatic atrophy, Pancreatitis, Paraesthesia oral, Rectal haemorrhage, Swollen tongue, Vomiting), **General disorders/Administration site conditions** (Application site reaction, Asthenia, Chills, Condition aggravated, Crepitations, Death, Drug interaction (see 2.1 *Overview of Safety / Subtitle – Drug Interactions***)**, Drug resistance, Embolia cutis medicamentosa, Enanthema, Fatigue, Feeling hot, Fibrosis, Generalised oedema, Hypothermia, Inflammation, Injection site haematoma, Malaise, Mucosal erosion, Mucosal inflammation, Multi-organ failure, Organ failure, Product substitution issue, Systemic inflammatory response syndrome, Ulcer), **Hepatobiliary disorders** (Acute hepatic failure, Gallbladder oedema, Hepatic cirrhosis, Hepatic failure, Hepatic steatosis, Hepatorenal syndrome, Hepatotoxicity, Jaundice, Perforation bile duct), **Immune system disorders** (Type I hypersensitivity, Type IV hypersensitivity reaction), **Infections/Infestations** (Aspergillosis, Candida osteomyelitis, Clostridium difficile colitis, Helicobacter infection, Lower respiratory tract infection, Muscle abscess, Necrotising fasciitis, Peritonitis, Post procedural infection, Respiratory tract infection, Sepsis, Septic shock, Urinary tract infection, Urosepsis), **Injury, Poisoning/Procedural complications** (Ankle fracture, Burns second degree, Complications of transplanted liver, Drug administration error, Fall, Fat embolism, Graft ischaemia, Incision site haemorrhage, Incorrect dose administered, Intentional overdose, Medication error, Multiple drug overdose, Multiple drug overdose intentional, Overdose, Post procedural bile leak, Post procedural haemorrhage, Toxicity to various agents, Ureteric injury, Wound haemorrhage, Wound secretion), **Investigations** (Blood alkaline phosphatase increased, Blood creatine phosphokinase increased, Blood fibrinogen increased, Blood iron increased, Blood lactate dehydrogenase increased, Blood lactic acid increased, Blood potassium increased, Blood sodium decreased, Blood urea increased, Electrocardiogram abnormal, Endoscopy abnormal, Fibrin D dimer increased, Free haemoglobin present, Haemoglobin decreased, International normalised ratio increased, Mean cell volume decreased, Nerve stimulation test abnormal, Prothrombin time prolonged, Red blood cell sedimentation rate increased, Urine output decreased, Weight decreased), **Metabolism/Nutrition disorders**

(Dehydration, Hyperkalaemia, Hyponatraemia, Iron deficiency, Lactic acidosis, Metabolic acidosis), **Musculoskeletal/Connective tissue disorders** (Ankylosing spondylitis, Arthralgia, Arthropathy, Back pain, Cartilage atrophy, Floppy infant, Foot deformity, Haemarthrosis, Muscle atrophy, Muscular weakness, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Myopathy, Rhabdomyolysis, Rheumatoid arthritis, Sensation of heaviness, Synovitis), **Neoplasms benign, malignant and unspecified (incl. cysts and polyps)** (Hepatic neoplasm, Lung neoplasm), **Nervous system disorders** (Areflexia, Brain stem infarction, Cerebral haemorrhage, Coma, Convulsion, Disturbance in attention, Dizziness, Encephalopathy, Hemiparesis, Hepatic encephalopathy, Intracranial pressure increased, Loss of consciousness, Optic neuritis, Posterior reversible encephalopathy syndrome, Speech disorder, Syncope), **Psychiatric disorders** (Aggression, Antisocial behaviour, Confusional state, Delirium, Depression suicidal, Disinhibition, Food aversion, Impulse-control disorder, Libido disorder, Restlessness), **Renal/Urinary disorders** (Chromaturia, Nephropathy, Renal disorder, Renal failure, Renal tubular necrosis, Urinary incontinence, Urinary retention), **Reproductive system/Breast disorders** (Galactorrhoea, Ovarian cyst ruptured, Suppressed lactation), **Respiratory/Thoracic/Mediastinal disorders** (Acquired diaphragmatic eventration, Acute respiratory distress syndrome, Atelectasis, Bronchospasm, Chronic obstructive pulmonary disease, Cough, Diaphragmatic paralysis, Dyspnoea, Dyspnoea exertional, Haemoptysis, Lung disorder, Orthopnoea, Pleural effusion, Pulmonary embolism, Pulmonary hypertension, Pulmonary oedema, Wheezing), **Skin/Subcutaneous tissue disorders** (Drug rash with eosinophilia and systemic symptoms, Erythema nodosum, Leukocytoclastic vasculitis, Lichen planus, Skin exfoliation, Skin haemorrhage, Skin hyperpigmentation, Skin necrosis), **Surgical/Medical procedures** (Resuscitation), **Vascular disorders** (Circulatory collapse, Deep vein thrombosis, Flushing, Haemorrhage, Hypotension, Neurogenic shock, Pallor, Shock, Shock haemorrhagic, Thrombosis), and **Pregnancy, Puerperium/Perinatal conditions** (Premature baby, Premature labour) have been described in serious ADR reports (see *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97]* from 30/09/2017 [Data Lock Point]).

In the period of this PSUR a total number of 387 medically confirmed serious unlisted adverse drug reactions were reported (see above). In spite of this, as discussed in detail, no change in characteristics of listed adverse drug reactions was observed and the safety profile of XXX has not changed in a fundamental way. The data described in this report did not change the risk/benefit balance of XXX. Therefore, no immediate actions are regarded as necessary. However, based on the review of safety data following PSUR evaluation and requirements from the regulatory authority relevant adverse drug reactions like cardiovascular adverse events, rhabdomyolysis, drug interactions (with colestipol, cholestyamine, methotrexate, phenytoin, CYP 2C9 inhibitors (e.g., voriconazol), sulfinpyrazone), gastrointestinal hemorrhage (particularly with perforation/ulceration), skin reactions including serious cases of injection site reactions, cases of hepatotoxicity including altered transaminase measurements, liver necrosis, jaundice, fulminant hepatitis with and without jaundice and liver failure, hepatobiliary disorders, skin reactions (dry skin, application site paresthesia), anastomotic leakage associated to XXX use, use of XXX in patients with influenza-related encephalitis or encephalopathy, nephrotoxicity caused by interaction between XXX with tenofovir, spontaneous hematoma/bruising, vasoconstriction and associated events like ischemic stroke, vasospastic angina and intestinal ischemia in relation to systemic/cutaneous application will be under close surveillance by the Pharmacovigilance Unit of MAH (see *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97] from 30/09/2017* [Data Lock Point]).

No signal justifying a change of the CCSI (Company Core Safety Information)/RSI (Reference Safety Information) arose from these mostly single unlisted symptoms. There is no evidence of any significant increase in the frequency of any adverse drug reaction due to XXX. All other reports mentioned above refer to adverse drug reactions from non-serious/serious cases that are already in this or in a similar form included in the CCSI (Company Core Safety Information), RSI (Reference Safety Information), ISE (Information Sheet for Experts) and PIL (Patient Information Leaflet).

Based on results of computer-assisted investigations for publications on the subject of adverse drug reactions, no new information regarding the benefit-risk-ratio of XXX could be found in the international literature (see *Appendix I*).

Drug Interactions

Oral co-administration of ciprofloxacin tablets (500 mg) with XXX tablets (50 mg) increased ciprofloxacin AUC and C_{max}, and reduced ciprofloxacin t_{max} and total body clearance (XXX *et al. 2016*). A co-administration of NSAID and aspirin may interfere with platelet inhibition at the beginning of a treatment with a decrease of XXX. This effect is lost after 4 days, suggesting that a regular daily co-administration of NSAID does not have an influence on platelet inhibition by aspirin (XXX - XXX *et al. 2016*).

The following new drug interactions (with ibuprofen, pantoprazole, dronedarone (leading to paroxysmal tachycardia, dyspnea, palpitations), carbamazepine (leading to hepatic encephalopathy, drug-induced liver injury, delirium, loss of consciousness, aggression, impulse-control disorder), adalimumab (leading to ruptured ovarian cyst, abdominal pain, peritoneal hemorrhage), enalapril (leading to hyperkalemia), amlodipine (leading to upper abdominal pain), fondaparinux (leading to hemarthrosis, hemorrhagic anaemia)) were identified. The drug interactions reported above will be further under close surveillance by MAH (see *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97] from 30/09/2017* [Data Lock Point]).

The international literature to date (time period of 01/01/2014 (2006) to 01/09/2018) contains no further reports or studies on drug interactions of XXX, and shows no further evidence of any drug-related interactions based on experimental clinical observations.

2.2 Summary of Safety

Spontaneous ADR reports, ADR reports from regulatory authorities and literature derived results (time period of 01/01/2014 (2006) to 01/09/2018) on clinical safety show no evidence of any significant increase in the frequency of any adverse drug reactions or drug interactions due to administration of the above-mentioned XXX preparations reported during the period covered by this clinical expert statement. No new information regarding the benefit-risk-ratio of XXX could be found in the international literature (see also *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97] from 30/09/2017* [Data Lock Point]).

Most ADR reports refer to side effects or drug interactions already included in the CCSI (Company Core Safety Information), RSI (Reference Safety Information), ISE (Information Sheet for Experts) and PIL (Patient Information Leaflet), either in this form or a similar form, besides following unlisted adverse drug reactions (Blood/Lymphatic system disorders (Anaemia, Anaemia haemolytic autoimmune, Coagulopathy, Disseminated intravascular coagulation, Haemolysis, Haemolytic uraemic syndrome, Haemorrhagic anaemia, Leukocytosis, Microcytic anaemia, Neutropenia, Spleen disorder), Cardiac disorders (Arrhythmia, Arteriosclerosis coronary artery, Atrial fibrillation, Bradycardia, Cardiac arrest, Cardiac disorder, Cardio-respiratory arrest, Cardio-respiratory distress, Coronary artery disease, Cyanosis, Kounis syndrome, Palpitations, Pericarditis, Tachycardia, Tachycardia paroxysmal), Congenital/Familial/Genetic disorders (Aplasia cutis congenita, Factor V deficiency, Factor VIII deficiency, Porphyria acute, Porphyria non-acute), Eye disorders (Abnormal sensation in eye, Conjunctival haemorrhage, Conjunctival oedema, Conjunctivitis, Eye pain, Eye swelling, Lacrimation increased, Ocular hypertension, Retinopathy hypertensive), Gastrointestinal disorders (Abdominal hernia, Abdominal pain, Abdominal rigidity, Ascites, Barrett's oesophagus, Colitis ischaemic, Colitis microscopic, Dental caries, Diaphragmatic hernia, Diarrhoea, Diverticular perforation, Duodenitis, Enteritis, Erosive oesophagitis, Faeces discoloured, Gastrointestinal disorder, Gastrointestinal tract mucosal pigmentation, Gastrooesophageal reflux disease, Hiatus hernia, Mallory-Weiss syndrome, Oedematous pancreatitis, Oesophageal ulcer, Oral discomfort, Oral pain, Palatal oedema, Pancreatic atrophy, Pancreatitis, Paraesthesia oral, Rectal haemorrhage, Swollen tongue, Vomiting), General disorders/Administration site conditions (Application site reaction, Asthenia, Chills, Condition aggravated, Crepitations, Death, Drug interaction (see 2.1 *Overview of Safety / Subtitle – Drug Interactions*), Drug resistance, Embolia cutis medicamentosa, Enanthema, Fatigue, Feeling hot, Fibrosis, Generalised oedema, Hypothermia, Inflammation, Injection site haematoma, Malaise, Mucosal erosion, Mucosal inflammation, Multi-organ failure, Organ failure, Product substitution issue, Systemic inflammatory response syndrome, Ulcer), Hepatobiliary disorders (Acute hepatic failure, Gallbladder oedema, Hepatic cirrhosis, Hepatic failure, Hepatic steatosis, Hepatorenal syndrome, Hepatotoxicity, Jaundice, Perforation bile duct), Immune system disorders (Type I hypersensitivity, Type IV hypersensitivity reaction), Infections/Infestations (Aspergillosis, Candida osteomyelitis, Clostridium difficile colitis, Helicobacter infection, Lower respiratory tract infection, Muscle abscess, Necrotising fasciitis, Peritonitis, Post procedural infection, Respiratory tract infection, Sepsis, Septic shock, Urinary tract infection, Urosepsis), Injury, Poisoning/Procedural complications (Ankle fracture, Burns second degree, Complications of transplanted liver, Drug administration error, Fall, Fat embolism, Graft ischaemia, Incision site haemorrhage, Incorrect dose administered, Intentional overdose, Medication error, Multiple drug overdose, Multiple drug overdose intentional, Overdose, Post procedural bile leak, Post procedural haemorrhage, Toxicity to various agents, Ureteric injury, Wound haemorrhage, Wound secretion), Investigations (Blood alkaline phosphatase increased, Blood creatine phosphokinase increased, Blood fibrinogen increased, Blood iron increased, Blood lactate dehydrogenase increased, Blood lactic acid increased, Blood potassium

increased, Blood sodium decreased, Blood urea increased, Electrocardiogram abnormal, Endoscopy abnormal, Fibrin D dimer increased, Free haemoglobin present, Haemoglobin decreased, International normalised ratio increased, Mean cell volume decreased, Nerve stimulation test abnormal, Prothrombin time prolonged, Red blood cell sedimentation rate increased, Urine output decreased, Weight decreased), Metabolism/Nutrition disorders (Dehydration, Hyperkalaemia, Hyponatraemia, Iron deficiency, Lactic acidosis, Metabolic acidosis), Musculoskeletal/Connective tissue disorders (Ankylosing spondylitis, Arthralgia, Arthropathy, Back pain, Cartilage atrophy, Floppy infant, Foot deformity, Haemarthrosis, Muscle atrophy, Muscular weakness, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Myopathy, Rhabdomyolysis, Rheumatoid arthritis, Sensation of heaviness, Synovitis), Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (Hepatic neoplasm, Lung neoplasm), Nervous system disorders (Areflexia, Brain stem infarction, Cerebral haemorrhage, Coma, Convulsion, Disturbance in attention, Dizziness, Encephalopathy, Hemiparesis, Hepatic encephalopathy, Intracranial pressure increased, Loss of consciousness, Optic neuritis, Posterior reversible encephalopathy syndrome, Speech disorder, Syncope), Psychiatric disorders (Aggression, Antisocial behaviour, Confusional state, Delirium, Depression suicidal, Disinhibition, Food aversion, Impulse-control disorder, Libido disorder, Restlessness), Renal/Urinary disorders (Chromaturia, Nephropathy, Renal disorder, Renal failure, Renal tubular necrosis, Urinary incontinence, Urinary retention), Reproductive system/Breast disorders (Galactorrhoea, Ovarian cyst ruptured, Suppressed lactation), Respiratory/Thoracic/Mediastinal disorders (Acquired diaphragmatic eventration, Acute respiratory distress syndrome, Atelectasis, Bronchospasm, Chronic obstructive pulmonary disease, Cough, Diaphragmatic paralysis, Dyspnoea, Dyspnoea exertional, Haemoptysis, Lung disorder, Orthopnoea, Pleural effusion, Pulmonary embolism, Pulmonary hypertension, Pulmonary oedema, Wheezing), Skin/Subcutaneous tissue disorders (Drug rash with eosinophilia and systemic symptoms, Erythema nodosum, Leukocytoclastic vasculitis, Lichen planus, Skin exfoliation, Skin haemorrhage, Skin hyperpigmentation, Skin necrosis), Surgical/Medical procedures (Resuscitation), Vascular disorders (Circulatory collapse, Deep vein thrombosis, Flushing, Haemorrhage, Hypotension, Neurogenic shock, Pallor, Shock, Shock haemorrhagic, Thrombosis), and Pregnancy, Puerperium/Perinatal conditions (Premature baby, Premature labour)) from serious ADR reports (see *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97] from 30/09/2017* [Data Lock Point]).

In summary, for none of the possible drug adverse reactions reported above an increased development during therapeutical use of XXX seems probable.

3 Conclusion

The evaluation on clinical efficacy and safety is based on the literature published from 01/01/2014 (2006) to 01/09/2018.

Based on the antiinflammatory, antipyretic, and analgesic properties, there is a definite place for XXX in the treatment of acute and chronic pain of many etiologies. XXX possesses antibacterial activity against both drug-sensitive and drug-resistant clinical isolates of *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli*, and *Mycobacterium spp*. in addition to its potent antiinflammatory activity.

The therapeutic effectiveness of XXX in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, renal/biliary colic, minor surgery, trauma, dysmenorrhea, actinic keratosis, and postoperative pain syndromes has been demonstrated sufficiently in a series of controlled studies.

An analgesic effect was demonstrated with the pretreatment/preoperative use of XXX for reducing the pain in children and adults undergoing various surgical procedures. XXX provides effective postoperative analgesia and reduces postoperative opioid consumption. At least similar effectiveness as compared with comparator pain relieving drugs has been demonstrated for XXX. Further trials studying topical XXX need to be of longer duration, be better reported and consider a broader spectrum of acute and chronic pain indications.

Alternatively, in the treatment of nocturnal polyuria and acute first-degree natural sunburn, XXX shows a good response. Oral XXX may be an alternative treatment choice in acute migraine attacks, although in most patients no complete absence of pain is achieved. Interestingly, the incidence of acute pancreatitis can be reduced by rectal XXX given immediately after endoscopic retrograde cholangiopancreatography. Furthermore, rectal XXX may also be a postoperative pain reliever for laparoscopic sterilization.

The review of the international literature revealed no data about unknown therapeutical effects or adverse drug reactions, and no new information regarding the benefit-risk-ratio of XXX could be found. No significant new efficacy or effectiveness information was revealed in relation to the approved indications. Data supposing an increased frequency of any adverse drug reactions or interactions due to XXX were not reported in the international literature or notified to the Pharmacovigilance Unit of MAH in the time period of this clinical assessment.

Since 01/90/2016 in 751 patients a total of 898 serious and 704 non-serious adverse drug reactions from spontaneous/regulatory (n=1026), clinical studies (n=23), literature (n=265) and non-healthcare professional (n=288) source were notified to the drug safety department of MAH in ratio to approximately 1.13 billion defined daily doses (corresponding with about 1.13 billion patient-days (patient exposure for oral/rectal forms of XXX, calculated with a mean daily dose of 100 mg according to the ATC Index (WHO)), 48.0 million treated patients (patient exposure for patenteral forms of XXX (corresponding with about 48.0 million of sold packages)), 16.7 million patients (patient exposure for topical forms of XXX (corresponding with about 16.7 million of sold packages)), 18.5 million defined daily doses (corresponding with about 18.5 million patient-days; patient exposure for transdermal patch forms, calculated with a mean daily dose of 280 mg). A total of 19 fatal cases from spontaneous/regulatory (n=11), clinical studies (n=0), literature (n=7) and non-healthcare professional (n=1) source were also notified to the drug safety department of MAH (see *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97] from 30/09/2017* [Data Lock Point]).

Furthermore, the current clinical data on XXX do not give any clues which would alter the past clinical evaluation (i.e. the clinical assessment of the risk-benefit ratio for the therapeutic

use of XXX). Therefore, it still remains evident that the general risk/benefit ratio of XXX formulations is positive and remained unchanged over time in the periods evaluated. Therefore, it can be stated that the risk-benefit ratio of XXX is positive and has been unchanged over time in the periods evaluated.

In the most recent and approved PSUR, CCSI, RSI, ISE and PIL of XXX formulations therapeutic indications, drug induced adverse effects, interactions and precautions are appropriately summarized. Most reports refer to adverse drug reactions already included, either in this form or a similar form, except for the serious unlisted adverse drug reactions according to the line-listing table (see 2.1 *Overview of Safety / Subtitle – Detailed Unlisted Adverse Drug Reactions;* 2.2 *Summary of Safety*).

With regard to place cardiovascular adverse events, rhabdomyolysis, drug interactions (with colestipol, cholestyamine, methotrexate, phenytoin, CYP 2C9 inhibitors (e.g., voriconazol), sulfinpyrazone), gastrointestinal hemorrhage (particularly with perforation/ulceration), skin reactions including serious cases of injection site reactions, cases of hepatotoxicity including altered transaminase measurements, liver necrosis, jaundice, fulminant hepatitis with and without jaundice and liver failure, hepatobiliary disorders, skin reactions (dry skin, application site paresthesia), anastomotic leakage associated to XXX use, use of XXX in patients with influenza-related encephalitis or encephalopathy, nephrotoxicity caused by interaction between XXX with tenofovir, spontaneous hematoma/bruising, vasoconstriction and associated events like ischemic stroke, vasospastic angina and intestinal ischemia as possible XXX-induced adverse drug reactions under close surveillance (see *Periodic Safety Update Report (PSUR) [59/90/97], Addendum to Clinical Overview (AddCO) [59/90/97] from 30/09/2017* [Data Lock Point]), no modifications in the CCSI, RSI, ISE and PIL are considered necessary.

On the basis of the comprehensive scientific documentation and the safety data currently available for this assessment, oral/parenteral/rectal/topical treatment with XXX can be judged as therapeutically appropriate, effective and safe in the authorized indications. Therefore, a further marketing authorization for XXX containing preparations can be approved and safely renewed on the basis of present knowledge.

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5 Enclosures

Appendix I: Results from international literature investigation for publications on therapeutical effectiveness and adverse drug reactions following administration of XXX