COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Morfine HCl 100 mg/10 ml Focus, Morfine HCl 200 mg/10 ml Focus and Morfine HCl 10 mg/ml Focus, solution for injection/infusion

(morphine hydrochloride trihydrate)

NL License RVG: 123453, 123455 & 123421

Date: 30 September 2021

This module reflects the scientific discussion for the approval of Morfine HCL Focus. The marketing authorisation was granted on 27 October 2020 For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

5-HT	5- hydroxytryptamine
AC50	half-maximal activity concentration
AMC	additional morphine consumption
API	average pain intensity
ASMF	Active Substance Master File
ATC	around the clock
BD	baseline doses mean
CA	caudal anaesthesia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	central nervous system
CPR	cardiopulmonary resuscitation
CSF	cerebrospinal fluid
CV	coefficient of variation
DOPAC	3,4-dihydroxyphenylacetic acid
ECG	electro cardiogram
e.d	epidural
ED50	median effective dose
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMG	electromyogram
ERA	Environmental Risk Assessment
FAAH	fatty acid amide hydrolase
FD	final doses mean
FLACC	Face, Legs, Activity, Cry, Consolability
FSH	follicle stimulating hormone
GABA	gamma amino butyric acid
HA	histamine
HCVR	Hypercapnic Ventilatory Response
HBF	hepatic blood flow
IAM	intra-articular.
ICH	International Conference of Harmonisation
i.v	intravenous
i.c.v.	intracerebroventricular
i.m	intramuscular
i.p.	intraperitoneal
ITM	intrathecal morphine
ITP	intrathecal placebo
ke0	equilibration rate constant

LA	local anaesthetic
LC	locus coeruleus
LH	luteinizing hormone
MAH	Marketing Authorisation Holder
MCR	morphine consumption reduction
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
NA	noradrenaline
NAS	Neonatal abstinence syndrome
NCA	nurse-controlled analgesia
NPS	numeric pain score
NM	normorphine
NRs	nonresponders
N/V	nausea/vomiting
OIBD	Opioid-induced bowel dysfunction
PAG	periaqueductal grey
PCA	patient-controlled analgesia.
PCS	plasma corticosterone
PFS	pre-filled syringes
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
Rs	responders
RCT	Randomised clinical trial
RD	respiratory depression
RH	Relative Humidity
ROP	Retinopathy of prematurity
RPS	Resting pain scores
RMP	Risk Management Plan
RRT	Rapid Response Team
SD	standard deviation
s.c	subcutaneous
SmPC	Summary of Product Characteristics
TD	Transdermal
TSE	Transmissible Spongiform Encephalopathy
VAS	visual analogue scale
WPI	worst pain intensity

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Morfine HCl 100 mg/10 ml Focus, Morfine HCl 200 mg/10 ml Focus and Morfine HCL 10 mg/ml Focus solution for injection/infusion, from Focus Care Pharmaceuticals B.V.

Morfine HCl 100 mg/10 ml Focus, Morfine HCl 200 mg/10 ml Focus and Morfine HCL 10 mg/ml Focus are indicated for severe acute and chronic pain, like tumour and postoperative pain.

A comprehensive description of the indications and posology is given in the SmPC.

Morphine has been widely marketed and used in the proposed indication for more than 10 years. Morphine is a well-established active substance in a variety of different pharmaceutical presentations. Reference is also made to a product called Vendal, which has been on the Austrian market since 1995, this product is considered the starting point of development for Morfine HCl Focus.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of morphine. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the community for at least ten years, with recognised efficacy and an acceptable level of safety.

II. QUALITY ASPECTS

II.1 Introduction

Morfine HCL Focus is a clear, colourless to slightly yellow solution.

Morfine HCl 100 mg/10 ml Focus contains as active substance 10 mg of morphine hydrochloride trihydrate per ml equivalent to 7.6 mg of morphine (base). Every injection vial contains 100 mg morphine hydrochloride trihydrate equivalent to 76 mg morphine.

Morfine HCl 200 mg/10 ml Focus contains as active substance 20 mg of morphine hydrochloride trihydrate per ml equivalent to 15.2 mg of morphine. Every injection vial contains 200 mg morphine hydrochloride trihydrate equivalent to 152 mg morphine.

Morfine HCl 10 mg/ml Focus contains as active substance 10 mg of morphine hydrochloride trihydrate per ml equivalent to 7.6 mg of morphine (base).

Morfine HCl Focus is packed in a 1 x 10 ml, 10 x 10 ml injection bottle made from type I PhEur-glass. The injection bottles are closed off with a teflon-coated bromobutyl stopper and are sealed with a white (100 mg/10 ml) or red (200 mg/ml) aluminium/polypropylene flip-off cap.

Morfine HCl 10 mg/ml Focus is packed in 10 x 1ml or 10 x 10 x 1ml clear, glass OPC-ampules.

The excipients for Morfine HCl 100 mg/10 ml Focus and Morfine HCl 200 mg/10 ml Focus are citric acid monohydrate, disodium edetate, hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment) and water for injection.

The excipients for Morfine HCl 10 mg/ml Focus are hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment) and water for injection.

II.2 Drug Substance

The active substance is morphine hydrochloride trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder or colourless, silky needles or cubical masses and is efflorescent in a dry atmosphere. Morphine hydrochloride is soluble in water, slightly soluble in ethanol (96%), practically insoluble in toluene. Polymorphic form and particle size of the active substance are not of relevance as the product is a solution.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia. The CEP documents have been submitted for both active substance manufacturers, this is considered to acceptable.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The MAH's active substance specification is in line with at least the Ph. Eur. monograph and the CEPs. The MAH's active substance specification is also a compilation of the active substance specifications of both manufacturers. The difference between the manufacturers regards the limits and methods for residual solvents. The control tests and specifications for the drug substance are acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches for each manufacturer.

Stability of drug substance

The active substance is stable for 48 months -no special storage conditions-, for the active substance stored in the proposed container closure systems. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEPs. The MAH provided additional data to confirm compliance of stored drug substance batches to the Ph. Eur. microbial purity requirements throughout shelf life.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The basis of the formulation development is a 'Vendal' product indicated as reference product/starting point for product development. No information is provided on 'Vendal' regarding exact quantitative compositions, authorisation date of the product and from which country samples were purchased. The MAH considers a bioavailability or bioequivalence study not required. Regarding sterile manufacturing process development: an 'overkill' steam autoclave sterilisation process (standard Ph. Eur. process) is used. The pharmaceutical development of the product has been sufficiently adequately performed. Comparative information with similar authorised products in view of the article 10a (well established use) application has been provided. Sufficient extractables studies results from the filters used in the process are provided. Extractables and leachables studies of drug product with the proposed Teflon coated bromobutyl rubber stoppers are provided, the results are within the limits. Adequate compatibility(/in-use stability) studies have been performed which sustain the shelf life after dilution with diluents and storage conditions as stated in the SmPC.

Manufacturing process

The manufacturing process consists of preparation of a bulk solution of the parental solution followed by bacterial retention, sterilisation, water loading, compounding, filtration, filling, autoclaving, inspection and labelling/packaging. The manufacturing process description contains sufficient details. Holding times are stated, which are sufficiently justified. Process validation data on the product have been presented for four full-scale production batches (two for each strength) in accordance with the relevant European guidelines. Process validation has been adequately performed, a process validation protocol is included for future re-validation of the process.

Control of excipients

The excipients generally comply with Ph. Eur. Requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, clarity and colour of solution, pH-value, relative density, extractable volume, identity, assay, related substances, sterility, bacterial endotoxins, sub-visible particles. The release and shelf-life specification for both strengths are acceptable. An adequate risk evaluation about possible contamination by nitrosamines is provided. Batch analytical data from the proposed production site have been

provided on two full scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for on two production scaled batches per strength stored during 60 months at 25°C/60% RH, 24 months at 30°C/35% RH and nine months at 40°C/75% RH in accordance with applicable European guidelines demonstrating the stability of the product for five years for the injection vials and four years for the ampoules. The batches were stored in the proposed glass vials. On basis of the data submitted, a shelf life of five years was granted for the injection vials and four years for the ampoules with no special temperature storage conditions.

In-use shelf-life: adequate justification is provided for the shelf life after dilution as stated in the SmPC. The shelf life statement in the SmPC for dilutions is adequate.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Morfine HCL Focus has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

III.1.1 Primary pharmacodynamics

Mode of action

Opioid effects are mediated through multiple opioid receptors. Opioid receptors can be found in various parts of the nociceptive system: in substantia gelatinosa, nuclei raphe of the medulla oblongata, the periaqueductal grey (PAG) matter and the medial thalamic nuclei. The receptors are also found in parts of the brain that control the motor sphere, the behaviour and the mood, or that take part in the neuroendocrine system. Outside the central nervous system (CNS), opioid receptors can be found predominantly in the small intestine, but also in other organs. Multiplicity of opioid receptors is a generally accepted concept to explain the different profiles of action of various agents that act on opioid receptors. Four main receptors exist designated with Greek letters of δ, κ, μ and σ. Furthermore, subpopulation of these main receptors have been proposed. Works in isolated animal tissues have provided a wealth of data (Jurna, 1992; Snyder, 1977; Goodman and Gilman's 10th Ed., 2001). Morphine produces

its major effects on the CNS by acting as agonist, particularly at μ receptors. However, it also has appreciable affinity for δ and κ receptors. Analgesia is predominantly associated with the μ and κ receptors. It is possible that analgesia and dependence may be due to the effects of morphine on μ1 receptor subtype, while respiratory depression and inhibition of gut motility may be due to actions on μ2 receptor subtype. Morphine, as a competitive agonist at the κ receptor, mediates spinal analgesia, miosis and sedation. As δ receptors are located mainly in the limbic system, it is assumed that their influence is predominantly on the affective reactions, mood and the behavioural response to pain (Jurna, 1992; Snyder, 1977; Goodman and Gilman's 10th Ed., 2001). Morphine is characterised by a high affinity for the opioid receptors and therefore represents a very potent analgesic. Morphine acts at both pre- and postsynaptic sites. At least three mechanisms appear to be involved. Opioid receptors on the terminals of the primary afferent nerves carrying nociceptive stimuli mediate inhibition of the release of excitatory neurotransmitters, including substance P. Neurons are hyperpolarised, thus suppressing spontaneous discharge and evoked responses. Morphine also antagonises the effects of exogenously administered substance P by exerting postsynaptic inhibitory actions on interneurons and on the output neurons of the spinothalamic tract that conveys nociceptive information to higher centres in brain (Jurna, 1992; Snyder, 1977; Goodman and Gilman's 10th Ed., 2001). The analgesic potency of morphine could be demonstrated by numerous bioassays, the results in animals being comparable to those in man.

Studies in rats

Morphine reduces painful sensation in rats. Dib (1985) has implanted an intrathecal cannula through which rats received either morphine or isotonic saline. Electrical nociceptive threshold rose significantly after injection of 10 μg morphine from 0.8 to 1.35 mA. Similar effects were seen in response to nociceptive stimulation by radiant heat (tail-flick test); intrathecally administered morphine (10 μg) produced rapid and complete analgesia within 2-3 minute of injection and there was also a significant rise of the tail-flick latency. The analgetic dose required to produce the maximum response in 50% of a group of animals exposed to radiation heat has been estimated to 2 mg morphine/kg after intravenous (i.v.) injection (Jackson, 1952). Maximal analgesia was reached within two minutes.

Studies in mice

Analgesic activity has also been investigated in mice by various techniques such as the tail flick test, hot plate method (top surface of an enclosed water-filled cooper bath with a surface temperature of 55°C), writhing syndrome (induced by intraperitoneal (i.p.) injection of 300mg/kg acetic acid 3% solution), and electroshock threshold. Morphine was effective in doses between 3.5 and 25 mg/kg p.o. dependent on the test (Witkin et al., 1961). Manning et al. (1994) performed a mapping study to determine where in the rat brain morphine acts to produce analgesia in the formalin test which is an animal model of prolonged pain associated with tissue injury. The results indicated that the primary sites of action of morphine are probably the posterior hypothalamic area and periaqueductal grey, with an additional contribution from regions innervated by tegmental dopamine cells. The antinociceptive mode of action of morphine probably involves also the central 5- hydroxytryptamine (5-HT) system. It is known that the full clinical effect of morphine is not seen if those neurones of the central nervous system which contain 5-HT have been inactivated. Morphine increases 5-HT turnover in brain and cord. Aiello-Malmberg et al. (1979) studied the effects of morphine on 5-HT release from the cerebral cortex of the cat. Brain 5-HT release was highly increased by

morphine hydrochloride 6 mg/kg i.v. The brain neuromodulator histamine (HA) is also thought to play an important role in morphine-induced antinociception. Some studies have shown that antinociceptive doses of systemic morphine increase extracellular HA levels in the rat periaqueductal grey (PAG). It was suggested that morphine acts on histaminergic neurons to cause HA release in PAG as part of its mechanism for pain relief (Barke & Hough, 1994).

III.1.2 Secondary pharmacodynamics

Effects on the cardiovascular system

Therapeutic doses produce peripheral vasodilatation and inhibition of baroceptor reflexes, and reduce peripheral resistance. The peripheral arteriolar and venous dilatation produced by morphine involves several mechanisms. Venous capacitance may be increased directly, whereas, indirectly, histamine release is implicated with morphine. Morphine provokes the release of histamine, which is associated with pruritus, urticaria, hypotension and decrease in systemic vascular resistance. The effects of histamine release by morphine are antagonised by H1 and H2 receptor antagonists without obtunding the increase in plasma histamine concentrations. Naloxone does not inhibit histamine release produced by morphine. Histamine release is therefore considered to be a displacement reaction, related to the dose and molar concentration of morphine and not a specific effect of opioids, related to analgesic potency. It is not determined by opioid receptor binding. Morphine also blunts the reflex vasoconstriction caused by increased pCO2 (Goodman and Gilman's 10th Ed., 2001). Effects on the myocardium are not significant, there is also no effect on electro cardiogram (ECG) or on the cerebral circulation. However, opioid-induced respiratory depression and CO2 retention can result in cerebral vasodilatation and an increase in cerebrospinal fluid pressure. Indirect effects may occur via sympathetic nervous system. Small doses are associated with increased plasma concentrations of adrenaline and noradrenaline, which increase heart rate and arterial pressure (Goodman and Gilman's 10th Ed., 2001). Henney et al. (1966) determined the effects of morphine on peripheral circulation in dogs. They demonstrated that the intravenous administration of morphine resulted in an immediate and significant decrease in total peripheral vascular resistance. The decrease was transient, and normal or increased resistance was noted 30 minute after administration. Morphine also increased the capacity of the total peripheral vascular compartment. The observed decreases in the venous tone indicated that the increased volume of blood was largely contained within capacitance vessels. The measured changes in both capacitance and venous tone occurred promptly and persisted throughout 30 minute of observation. The experiments indicated that increased capacitance and venous pooling are important effects of morphine on the circulation.

Effects on respiration and cough

Morphine depresses respiration, at least in part by direct effect on the pontine and bulbar brainstem respiratory centres. The primary mechanism of respiratory depression involves a reduction of the responsiveness of the brain respiratory centres to increasing concentrations of inhaled carbon dioxide. The pontine and medullary centres involved in regulating respiratory rhythmicity and the responsiveness of medullary respiratory centres to electrical stimuli are also depressed. The respiratory depressant effects are dose-related (in man, death from morphine poisoning is nearly always due to respiratory arrest). Therapeutic doses depress all phases of respiratory activity and may also produce irregular and periodic breathing). The diminished respiratory volume is due primarily to a slower breathing rate.

Maximal respiratory depression occurs within 5-10 minute after i.v. administration of morphine or within 30 or 90 minute following intramuscular (i.m.) or subcutaneous (s.c.) administration, respectively. Respiratory minute volume may be reduced for as long as four to five hours (Goodman and Gilman's 10th Ed., 2001). Morphine also depresses the cough reflex, at least in part by a direct effect on cough centre in the medulla. There is, however, no obligatory relationship between depression of respiration and depression of coughing (Goodman and Gilman's 10th Ed., 2001). With increasing doses of morphine (from 0.4 to 1.6 mg/kg), a significant drop in respiratory frequency, with a relative shortening of inspiration in comparison with expiration, was observed in rabbits (Bucher et al., 1973). The mean intrapleural pressure decrease per breath became also significantly smaller, whereas the maximal pressure decrease remained nearly unaltered. Infant and young macaque monkeys appeared to be less sensitive to the respiratory depressant effect of morphine than humans (Lynn et al., 1991). Both new-born and three- to four- month old monkeys showed variable but usually mild respiratory depression after intravenous morphine (tailored bolus dosing of morphine sulphate 0.1-0.25 mg/kg/every two minutes), as reflected by the small increases in PaCO2 which persisted for the 6h duration of the study. The respiratory effects measured by PaCO2 and respiratory rate did not correlate with declining serum or cerebrospinal fluid morphine levels. Morphine has pronounced effects on the gastro-intestinal tract which results in a reduction of the gastrointestinal motility leading to constipation. Longitudinal propulsive peristalsis is reduced, whereas contractility and sphincter tone are increased. Morphine usually decreases the secretion of hydrochloric acid in stomach, although stimulation is sometimes evident. Activation of opioid receptors on parietal cells enhances secretion, but indirect effects, including increased secretion of somatostatin from the pancreas and reduced release of acetylcholine, appear to be dominant in most circumstances. Decreased lower oesophageal pressure and increased likelihood of oesophageal reflux has been demonstrated. Relatively low doses of morphine decrease gastric motility, thereby prolonging the time and reducing the rate of gastric emptying. The tone of the antral portion of the stomach and of the first part of the duodenum is increased (Goodman and Gilman's 10th Ed., 2001). Morphine diminishes intestinal secretion and delays digestion of food in the small intestine. Resting tone is increased, and periodic spasms are observed. The amplitude of the nonpropulsive type of rhythmic, segmental contractions is usually enhanced, but propulsive contractions are markedly decreased. The upper part of the small intestine (duodenum) is more affected than the ileum. Water is absorbed more completely because of the delayed passage of the bowel contents and intestinal secretion decreased; this increases the viscosity of the bowel contents. Morphine inhibits the transfer of fluid and electrolytes into the lumen by naloxone-sensitive actions on the intestinal mucosa and within the CNS. Enterocytes may possess opioid receptors, but this hypothesis is controversial. However, it is clear that morphine exerts important effects on the submucosal plexus that lead to a decrease in the basal secretion by enterocytes and inhibition of the stimulatory effects of acetylcholine, prostaglandin E2 and vasoactive intestinal peptide (Goodman and Gilman's 10th Ed., 2001). Propulsive peristaltic waves in the colon are diminished or abolished after morphine administration, and tone is increased to the point of spasm. The resulting delay in the passage of the contents causes considerable desiccation of the faeces, which in turn, retards its advance through the colon. The amplitude of the nonpropulsive type of rhythmic contractions of the colon is usually enhanced. The tone of the anal sphincter is greatly augmented, and the reflex relaxation response to rectal distension is reduced. These actions, combined with inattention to the normal sensory stimuli for the defecation reflex owing to the central actions of the drug,

contribute to morphine-induced constipation (Goodman and Gilman's 10th Ed., 2001). The effects of s.c. administered morphine hydrochloride on gastric emptying and gastrointestinal propulsion were studied in male mice (Scheufler & Zetler, 1981). Drug effects were evaluated by the movement of Indian ink administered directly into the stomach after drug injection. Morphine inhibited both gastrointestinal propulsion (ED50 = 2.1 µmol/kg) and gastric emptying (ED50 = 43 µmol/kg). Naloxone reversed both effects of morphine. In other experiments in mice, doses of 5 mg/kg s.c. caused some reduction in motility 30min after application which returned to normal after 90minutes. Higher doses of 10 mg/kg caused drastic reductions in motility for 90 minute (Witkin et al., 1961). Studying the morphine tissue levels and reduction of gastrointestinal transit in rats, Bianchi et al. (1983) have supported a local rather than a CNS-mediated origin of morphine-induced constipation and a possible dissociation of morphine analgesia from its intestinal side effect in animals. The gastrointestinal effects of morphine can also be concluded from the fact that animals which are addicted to morphine suffer from a diarrhoea after sudden discontinuation of the morphine medication, the intensity of such diarrhoea being an indirect measure for the degree of the physical addiction. For example, it was shown that morphine-dependent rats rapidly developed complete tolerance to the delayed intestinal transit of a meal observed after acute morphine administration. Abrupt withdrawal from morphine (induced by naloxone) accelerated the intestinal transit with persistent diarrhoea (Brown et al., 1988). Morphine produces nausea and vomiting by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. The effect is dose-related and tolerance to it develops rapidly. The nauseant and emetic effects of morphine are markedly enhanced by vestibular stimulation, and morphine produces an increase in vestibular sensitivity. The emetic effect of morphine may be treated by anticholinergics and phenothiazines, especially those which are antagonists at dopamine receptors (Goodman and Gilman's 10th Ed., 2001).

Metabolic effects

The effect of acute and chronic morphine treatment on i.v. glucose tolerance tests was investigated in mice (Chan & Dai, 1989). It was found that neither acute nor chronic morphine treatment affected the serum glucose disappearance with time after i.v. glucose loading, indicating that morphine has no significant effect on glucose tolerance. Analysis of hepatic glycogen and glucose levels in morphine-dependent mice revealed that morphine treatment might have some effects on glucose metabolism, when resulting in significantly lowered hepatic fasting glucose level. On the other hand, hyperglycaemic effect of acute morphine administration has been demonstrated in dogs, rats, mice and human. It is not clear whether this is the result of increased glucose production and/or decreased glucose utilization. Molina et al. (1994) have provided evidence that the hyperglycaemic effects of morphine are regulated by the central nervous system and appear to be the result of enhanced rates of hepatic glucose production. In rats, the authors observed significant rise in plasma glucose (+23%), hepatic glucose production (+27-61%) and whole body glucose utilization (+31-61%) within 60 minute of intracerebroventricular (i.c.v.) morphine administration. These effects were enhanced with glucuronidation. Morphine also inhibited pancreatic glucose-stimulated insulin release. Finally, the hypoglycaemic effect of morphine injected intrathecally was studied in mice (White et al., 1993). Much lower glycogen content in muscle and depletion of liver glycogen occurred in morphine-treated mice. Spinal transection completely inhibited the hypoglycaemic effect of morphine, whereas adrenalectomy caused no inhibition. The

hypoglycaemic effects of morphine appeared to be largely due to an increased glucose uptake by muscles.

Effects on the genitourinary system

Morphine causes a dose-dependent reduction in the outflow of urine and changes of electrolyte composition. Therapeutic doses of morphine may increase the tone and amplitude of contractions of the ureter, although the response is quite variable. When the antidiuretic effects of the drug are prominent and urine flow decreases, the ureter may become quiescent. Morphine inhibits the urinary voiding reflex by decreasing the central inhibition of detrusor tone, and both the tone of the external sphincter and the volume of the bladder are increased. Retention of urine is a frequent finding. Naloxone antagonises these effects, promoting increase in detrusor contractility with reduction in functional bladder capacity. The influence on the autonomic control of bladder function may be mediated through stimulation of receptors in brain or thoracic spinal cord. Tolerance develops to these effects on the bladder (Goodman and Gilman's 10th Ed., 2001). The nature of morphine-induced urinary retention was studied in anesthetised rats in which the bladder contraction accompanying micturition could be observed (Kontani & Kawabata, 1988). The urinary retention induced by systemically injected morphine was considered to result from inhibition of bladder function mediated via opioid receptors of micturition centres in supraspinal and spinal regions. Huidobro et al. (1979, 1981) found a dose-dependent antidiuresis associated with decreased excretion of urine electrolytes caused by morphine. The decrease in the urine electrolytes was accompanied by a modest, but significant increase in blood electrolytes. Tolerance developed to the antidiuresis, as single injection reduced renal clearance of endogenous creatinine already by about 50%. However, clearance values rapidly returned to normal when slow-release morphine-pellets were implanted. They interpreted decrease in creatinine clearance primarily as result of reduction in the rate of glomerular filtration via central and/or peripheral opioid mechanism. Therapeutic doses of morphine may prolong the labour. If the uterus has been made hyperactive by oxytocics, morphine tends to restore tone, frequency, and amplitude of contractions to normal. In addition, central effects of morphine may affect the degree to which the parturient is able to cooperate in the delivery. Failure to ejaculate after lumbar extradural morphine has been described. Similar effect has been found in rats after intrathecal morphine. defects have been correlated and changes in the weight of testes, prostate, seminal vesicles described. Morphine inhibits also the release of gonadotropin-releasing hormone, thus decreasing plasma levels of luteinizing hormone and follicle-stimulating hormone. James et al. (1980) correlated the changes in pituitary-testicular morphology with effects of chronic morphine doses of 50 mg/kg/day for up to 9 weeks s.c. with effects on gonadotropin and androgen secretion in rats. Morphine decreased serum LH and testosterone concentrations and reduced secondary sex organ weights. Differential staining techniques revealed modified secretory activity of pituitary gonadotrophic cells. All stages of spermatogenesis were found in testicular sections, but quantitative reductions in spermatogenic cell populations were found. All the effects were reversed by drug withdrawal. Spinal opiates appear to affect sexual performance primarily by modifying sympathetic responses to sexual stimulation. Wiesenfeld-Hallin & Södersten (1984) reported that the intrathecal injection of morphine into female ovariectomised rats pre-treated with oestradiol benzoate and progesterone inhibited sexual receptivity, while injection of the opiate receptor antagonist naloxone enhanced it. Similarly, intrathecal injection of morphine increased while injection of naloxone decreased the number of intromissions before ejaculation in male rat. The results indicated that sexual behaviour

may be influenced by spinal opiates. Agmo et al. (1994) analysed the effects of morphine on sexual behaviour in male rabbits and evaluated the role of central and peripheral opioid receptors. Morphine was found to inhibit sexual behaviour in a dose dependent way. It was concluded that the inhibitory effects of morphine are localised within the central nervous system and might be mediated by the μ receptors. The hippocampal pyramidal cells represent the main cerebral area where morphine produces the excitatory-epileptogenic effects. Several mechanisms appear to be involved. The epileptogenic effects seem to be mediated by a prevalent interaction at the K opiate receptors, while the excitatory effects depend upon an influence on both μ and δ receptors (Sagratella & Scotti-de-Carolis, 1993). The excitatory effects probably result from inhibition of the release of gamma amino butyric acid (GABA) by interneurons. However, convulsions occur only at doses far in excess of those required to produce profound analgesia (300 mg/kg of morphine i.p. was observed to produce convulsions in adult animals). Naloxone is more potent in antagonizing convulsions produced by morphine than produced by some other opioids. Anticonvulsant agents may not always be effective in suppressing opioid-induced seizures. Intraperitoneal administration of morphine hydrochloride at doses of 300 mg/kg produced analgesia, catalepsy, and electrographic spiking in rats that developed into electrographic seizure patterns after approx. 2.5 hours (Frenk et al., 1982). In contrast, naltrexone (12 mg/kg) reversed analgesia and catalepsy, and diminished electrographic spiking; it precipitated electrographic seizure activity similar to that observed following i.p. morphine alone. These seizures were accompanied by behavioural convulsions. No tolerance to these seizures developed with repeated coadministration of morphine and naltrexone or in morphine tolerant rats, but rather potentiation was observed. It was concluded that two different epileptogenic mechanisms are activated. One is opiate in nature, as can be deduced from the ability of naltrexone to reverse epileptic spiking activity seen after high doses of morphine, and the other non-opiate and neither reversed by opiate antagonist nor undergoing tolerance with chronic opiate treatment. These epileptogenic effects were suggested to be mediated by glycinergic and GABAergic systems. Non-specific excitatory effects of morphine develop earlier and are more pronounced than specific effects (Van Praag & Frenk, 1992).

Effects on behaviour

The mechanism by which opioids produce euphoria, tranquillity, and other alterations of mood is not entirely clear. Microinjection of opioids into ventral tegmentum activates dopaminergic neurons that project to nucleus accumbens; this pathway is postulated to be a critical element in the reinforcing effects of opioids and opioid-induced euphoria. Activation of mesolimbic dopaminergic (DA) system by morphine can elicit positive reinforcing effect in the rodent. The partial involvement of μ-opioid receptors in psychic dependence on morphine was suggested. Indeed, pre-treatment with μ-opioid antagonists is capable of abolishing the reinforcing properties of morphine. However, the administration of dopaminergic antagonists does not consistently prevent reinforcing effects of opioids, thus some nondopaminergic mechanisms may also play role. The neural systems mediating opioid reinforcement in the ventral tegmentum appear to be distinct from those involved in classical manifestation of physical dependence and analgesia (Goodman and Gilman's 10th Ed., 2001).

Morphine-induced locomotion and hyperactivity

In addition to analgesia, an important property of morphine is the ability to stimulate motor activity in rodents. However, in adult rats, morphine has a triphasic effect on activity:

hyperactivity at very low doses, hypoactivity that culminates in catatonia accompanied by muscular rigidity at higher doses which is mediated by μ-receptors and reversed by naloxone, and hyper alternating with hypoactivity at the highest doses. Hyperactivity following low doses of morphine is likely to be mediated by K-receptors (absent during the first two weeks in new-born rats, since K-receptors appear only in the 2. postnatal week) and activation of mesolimbic DA system. This also indicates that morphine is less toxic in new-borns than suggested previously (van Praag & Frenk, 1992). Anagnostakis et al. (1992) investigated the effects of morphine hydrochloride (5.0, 7.5, 100 μg/0.5 μl) on locomotor activity when administered intrapallidally (bilateral microinjections; three pallidal areas tested - dorsal, medial, ventral). The results showed that morphine injected into different parts of globus pallidus produced increased locomotor activity which is abolished by naloxone pre-treatment. This increase was dose-dependent and also significantly different between the three pallidal regions (medial/dorsal greater than ventral). The results have provided evidence that pallidum is involved to a different degree in the increased motor activity mediated by opiate receptors.

Morphine-induced rigidity

Morphine may cause opisthotonus, rigidity, spasticity, catalepsy, circling and stereotypical behaviour in rats and other animals (high doses can produce muscular rigidity also in man). These effects are probably related to actions at opioid receptors in substantia nigra and striatum, and involve interactions with both dopaminergic and GABA-ergic neurons. Motility, rigidity and turnover of dopamine in the striatum after administration of morphine was studied in rats (Genc et al., 1983). Administration of morphine (30 mg/kg i.p.) induced strong muscular rigidity, when measured as tonic activity in the electromyogram (EMG). The effect was maximal after one hour and disappeared during the fourth hour. The locomotor activity, on the other hand, disappeared after 30 minutes (with almost complete akinesia lasting for about 2.5 hours) and reappeared during the fourth hour, followed by a locomotor stimulation (max. after 4.5 hours). Striatal lesions produced with kainic acid did not affect the akinesia, except by slightly prolonging this effect, and did not influence the delayed locomotor stimulation. These lesions did not inhibit, but, enhanced the increase in dopamine turnover in the striatum. This increase together with the delayed locomotor stimulation ought to be regarded as actions of morphine on sites different from those mediating muscular rigidity. Melzacka et al. (1985) compared the pharmacokinetics of morphine with its ability to increase striatal dopamine turnover (estimated by increase in 3,4-Dihydroxyphenylacetic acid or DOPAC concentration) and to produce the development of muscular rigidity (investigated as a tonic activity in the electromyogram). They also observed that the muscular rigidity induced by systemic administration of morphine (15 mg/kg i.p.) resulted from the drug interaction with striatal opioid receptors, whereas the morphine-induced increase in the striatal dopamine turnover is, at least in part, mediated by the opioid receptors located in the substantia nigra. The time course of muscular rigidity was different both from the time course of the effect of morphine on striatal dopamine turnover and of morphine concentration in striatum which might be a result of interference of a dopaminergic activation with the rigidity. The activation of the dopaminergic neurones probably occurs via opioid receptors in substantia nigra and is likely to antagonize rigidity. There was evidence that receptors mediating the activation of dopaminergic neurones are slightly more sensitive to morphine than those mediating rigidity. As described above, acute administration of morphine produces akinesia and muscular rigidity in rats. This effect is followed by signs of locomotor activation and stereotype behaviour. After repeated administration of morphine, tolerance to akinesia develops, with an earlier and

more pronounced appearance of locomotor activation and stereotypies. In rats the development of tolerance to the muscular rigidity produced by morphine was studied by Themann et al. (1986). They suggested that rigidity can be antagonised by another process leading to dopaminergic activation in striatum. The rapid alternations of rigidity observed might be due to rapid shifts in the predominance of various DA innervated structures.
Tolerance to morphine-induced catalepsy in rats (Rose et al., 1979) was noted after twice daily administration of morphine hydrochloride (10 mg/kg, i.p.), tolerance being discernible after the third injection and complete after the 11th injection. With development of tolerance, morphine-induced effects on striatal acetylcholine and cholinesterase (catalepsy was associated with enhanced striatal acetylcholine levels and reduced cholinesterase activity) were progressively reversed, confirming striatal cholinergic involvement in morphine-induced catalepsy. Development of tolerance and physical dependence The development of tolerance and physical dependence with repeated use of morphine is common and a characteristic clinical phenomenon. The tolerance and dependence on morphine appear more or less simultaneously. The development of tolerance to the analgesic effects may be related to modification of receptor systems in the central nervous system. Studies have revealed that there are two kinds of opioid tolerance, namely acute opioid tolerance and chronic opioid tolerance (Wang & Ho, 1994). Acute tolerance to the anaesthetic effect of opioids has been demonstrated in animal experiments. Acute morphine tolerance may develop within four hours after single bolus. Chronic tolerance may develop with a latency period of eight to ten days and last for a long period. The characteristics of acute tolerance may differ from those of chronic opioid tolerance. Patient-controlled analgesia with or without basal infusion of morphine is now commonly used for pain relief. The phenomenon of acute tolerance to analgesic effect observed in animals might well be expected in patients. Studies in which a constant rate of morphine was given by i.v. infusion for eight hours demonstrated a profound decrease of morphine analgesia with time both in dogs and in rats. The slower decline of morphine in brain concentration as compared to recovery from the analgesic effect may indicate that even a single injection of morphine leads to the development of acute tolerance, thus shortening the duration of analgesia. Kissin et al. (1991) studied this decline of the analgesic effect of morphine with continuous infusion or that after single s.c. injection in rats. With constant rate morphine infusion, the peak effect of analgesia could not be maintained, it began to decrease four hours after start of infusion, and was profoundly reduced after eight hours, despite the absence of any decrease in morphine brain concentration. With single morphine injection, recovery from analgesia developed at much faster rate than morphine brain concentration declined. This absence of correlation between analgesia and morphine brain concentration both with constant rate morphine infusion and after single injection suggested the development of acute tolerance being pharmacodynamic in nature. Withdrawal The abrupt discontinuation of morphine administration typically results in loss of the tolerance and at the same time emergence of the withdrawal syndrome. Withdrawal symptomatology includes both physiological effects such as nausea, gastrointestinal disturbances (diarrhoea) and flu-like state and motivational aspects, in particular aversive stimulus or negatively reinforcing effects. In rodent models the physical withdrawal syndrome includes whole-body shakes, diarrhoea, escape jumps, teeth chattering, salivation and irritability. Time course for the development of tolerance, dependence and abstinence was investigated using a rat model (Gold et al., 1994). The results have suggested that the phenomena of tolerance and dependence develop concurrently with a similar time course during which plasma morphine concentrations remain quite stable. Abrupt withdrawal in

chronically dependent monkeys (Domino et al., 1987) caused symptoms which severity correlated negatively with the falling plasma morphine concentrations. Thus, significant morphine withdrawal symptoms arose despite measurable morphine plasma concentrations and the relationship between plasma concentrations and withdrawal might be quantified according to a linear pharmacokinetic model. Kishioka et al. (1994) have confirmed that plasma corticosterone (PCS) elevation is a quantitative sign of naloxone-precipitated morphine withdrawal and elevation is indicative of the degree of morphine physical dependence in rats. Naloxone elevated PCS levels in a dose-dependent manner in all groups treated with morphine, and elevation was correlated with the number of days of morphine treatment. Many neuronal systems are involved in the mechanism underlying morphine withdrawal events. The central noradrenergic system has been hypothesised to be one of the final pathways which are activated in the expression of morphine withdrawal signs (Funada et al., 1994). For example, the firing rate of locus coeruleus (LC) noradrenergic neurons, and the turnover of noradrenaline (NA) in the cerebral cortex that projects from the LC have been reported to increase during morphine withdrawal. Furthermore, it was reported that cortical NA turnover increased during naloxone-precipitated withdrawal in morphine-dependent mice. The blocking effects of μ-antagonists indicated that naloxone-precipitated jumping may be mediated predominantly by α1-adrenoceptors, while naloxone-precipitated "wet dog" shakes may be mediated by both α1- and α2-adrenoceptors. Profound decrease of mesolimbic dopaminergic spontaneous neuronal activity was recorded in unanaesthetised rats withdrawn from chronic (15 days) morphine administration (Diana et al., 1995). Considering the role of the mesolimbic dopaminergic system in the reinforcing properties of opioids, its tonically reduced activity during the morphine withdrawal syndrome may provide the neurobiological correlate of the dysphoric state associated with morphine withdrawal. Another study (Suzuki et al., 1992) investigated the role of μ-receptors in naloxone precipitated withdrawal. The results suggested that weight loss, diarrhoea and ptosis might be mediated by μ2 and/or δ-opioid receptor, while jumping and body shakes might be mediated by μ1-opioid receptors. They also supported that the weight loss might mainly result from diarrhoea. The role of cholinergic neurons in the expression of certain morphine withdrawal symptoms has also been recognised for many years. Central cholinergic neurons are susceptible to inhibition by opiates and during withdrawal their firing rates are enhanced. When withdrawal syndrome is precipitated by nalorphine, there is an explosive increase in the amount of brain's free acetylcholine. Morphine abstinence syndrome might be attributable to this presumed sudden release of acetylcholine. It was also found that a significant antiwithdrawal action could be produced through both inhibition of supraspinal and spinal cholinergic neurons. It was suggested that different muscarinic systems, possibly different receptor subtypes, mediate the expression of morphine withdrawal symptoms within the regions of CNS.

Concluding on the presented pharmacodynamics literature: briefly, in vivo and/or in vitro, morphine is known to exert effects on peripheral vasodilatation and inhibition of baroceptor reflexes, and reduce peripheral resistance; depress respiration and cough reflexes; has effects on the gastro-intestinal tract, which results in a reduction of the gastrointestinal motility leading to constipation; produces nausea and vomiting by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla; affects glucose regulation; effects of outflow of urine and changes of electrolyte composition; decreased plasma testosterone, loss of libido, impotence, reduced ejaculate volume, and sperm motility; excitatory and behavioural effects, altered locomotion and hyperactivity; rigidity; and

development of tolerance and withdrawal. No pharmacodynamic drug interactions have been discussed by the MAH. Given the extensive clinical experience, this is accepted.

III.2 Pharmacokinetics

Absorption after single-dose administration

In general, morphine is absorbed from all routes of administration, except transdermal. Morphine is rapidly, but variably, absorbed from the gastrointestinal tract following oral (p.o.) administration; absorption through the rectal mucosa is adequate. It is also readily absorbed after s.c. or i.m. injection. Peak plasma levels occur within 15-20 minute of i.m. and s.c. administration, and within 30-120 minute following oral dose. Peak levels after single oral administration are much lower than after parenteral routes. The mean bioavailability of oral preparations of morphine is only about 25% within the range of 10-50%. These data indicate that the mean oral/parenteral ratio for an equivalent pain relieving effect is three, but the extremes in this ratio are two to ten. The reason of the poor oral bioavailability is the extensive hepatic presystemic metabolism of morphine. Hepatic insufficiency decreases the first-pass effect and therefore increases the bioavailability of oral morphine. In addition, animal studies have shown that morphine is metabolised by the intestinal mucosa prior to absorption. In rodents, the gut may be responsible for up to 2/3 of the presystemic metabolism of morphine, the remaining 1/3 is metabolised by liver (Iwamoto & Klaassen, 1977). In this study, morphine was almost completely absorbed from the gastrointestinal tract; the route of administration had no effect on plasma half-life (about 115 min) of unchanged morphine. In contrast, the area under the plasma concentration vs. time curve for morphine after oral administration was only about 18%, and after intraportal administration about 40% of that observed after intravenous administration. In another study, Katagiri et al. (1988) have confirmed that systemic bioavailability of morphine is almost complete (90%) after rectal dosage, avoiding the first-pass metabolism, compared with poor oral bioavailability (10%). Absorption after repeated administration: With repeated oral administration, there is a greater contribution of morphine-6-glucuronide to the analgesic effect as well as of the enterohepatic circulation of morphine and its metabolites which explains an oral/parenteral potency ratio closer to 1:2 or 1:3 (Hanks et al., 1987). Vetulani et al. (1983) have studied the pharmacokinetics of morphine in rats given single high doses of morphine, and of two types (constant dose or increasing dose) of chronic treatment. The results indicated that pharmacokinetics of morphine changed after chronic treatment, and these changes were depending on the dosage schedule. Treatment with constant doses resulted in slowing down the elimination of morphine, resulting in higher concentrations and AUC values than after single dose. Increasing doses induced a more rapid disappearance of morphine from the body. Morphine given in constant doses is present in the body for a longer time than after increasing doses. The data also indicated that plasma concentration of morphine may not reflect drug levels in tissues, particularly in central nervous system.

Distribution

After absorption, morphine is readily distributed throughout the body to highly perfused tissues, such as lungs, kidney, liver, spleen and muscles. Morphine is relatively hydrophilic and therefore has a lower volume of distribution than the majority of the other opioid drugs. The apparent volume of distribution at steady state is usually 2-3 l/kg. Animal studies have shown that the highest levels of morphine occur in liver, kidney, lung, heart, cerebellum, spleen,

thymus, adrenal glands, and thyroidea. With therapeutic doses, morphine is bound to plasma proteins only to the extent of 25-35%. Morphine binds to albumin and gammaglobulin. Binding is independent of dose, but depending on protein concentration. Morphine plasma pharmacokinetics were not substantially altered by different schedules of administration in rhesus monkeys (Greene et al., 1987). Steady-state morphine plasma concentrations were directly proportional to infusion rate. No accumulation of morphine was observed. Steady-state cerebrospinal fluid (CSF) morphine concentrations were lower than free morphine plasma concentrations, suggesting that morphine efflux exceeds morphine influx in the brain although other factors (metabolism in CNS, regional concentration differences) might also explain this observation. Although the primary site of action of morphine is in the CNS, animal studies have indicated that there is a significant blood-brain-barrier controlling the entry of morphine into CNS. Morphine is significantly more potent when administered intraventricularly than after systemic administration. A recent study has revealed that the concentration of morphine in CSF samples collected following 10 mg i.m. dose was between one and 30µg/l. Further, an apparent equilibrium between CSF and blood occurred after three hours with a mean CSF/plasma ratio of 0.89. The ability of morphine to pass the blood-brain-barrier was studied in rats. About 30 seconds after i.v. injection of radioactive morphine, approximately 90% of morphine disappeared from blood plasma. At no time during 32 minutes examination period, the morphine concentration in the brain was more than 6% of the mean body concentration (Oldendorf et al., 1972). Fuller et al. (1988) have examined regional morphine accumulation in the rat in 8 brain areas (cerebral cortex, hippocampus, striatum, midbrain, hypothalamus, thalamus, medulla oblongata and cerebellum) following either single dose or incremental doses administered by intraperitoneal injection. Results indicated a dose-dependent, differential accumulation of morphine in different brain regions following incremental morphine administration; three distinct uptake profiles were obtained, with cerebellum, hippocampus, medulla and cortex showing roughly linear accumulation, midbrain, striatum and thalamus showing nonlinear accumulation, and hypothalamus showing significantly higher absolute morphine levels than other regions. In several studies, no differences in the distribution of morphine were observed in plasma and various tissues of morphine tolerant animals, when compared to non-tolerant controls. However, other studies comparing old and young age groups of animals, demonstrated that the altered pharmacological responses to morphine may be related to the higher concentrations of morphine in the central nervous system of older animals, which in turn may be related to the differences in the blood-brain-barrier to morphine in the two age groups. Finally, Gabrielsson et al. (1983) examined the disposition of morphine in pregnant rats. Morphine was taken up readily by the foetus via the placenta, with morphine concentrations in the foetal plasma being 1.5 times higher than in the plasma of the mother animals, and in the foetal brain being four times higher than in the brain of the mother animals 20-30 minutes after application. The relatively higher concentration in the cerebral tissue of foetus is explained by the low degree of lipophilic substances (e.g. myelin) in the undeveloped brain. Morphine also passes over to the mother milk (in human breast milk <1% of any dose).

Protein binding

Protein binding of morphine was studied in horses by Combie et al. (1983). The pharmacokinetic properties of morphine were described by a three-compartment model, with a $t_{1/2}$ of 2.5 minutes (human 0.9-17 minutes), $t_{1/2}$ of 87.9 minutes (human 78-204 minutes), and $t_{1/2}$ of 56.3 hours (human 10-44 hours). Shortly after i.v. administration, the morphine

concentration in the plasma amounted to 624 ng/ml. Binding to equine serum proteins was independent over a wide range of drug concentrations and averaged 31.6% (rhesus monkeys 30%, man 20.8-35.2%, variation among 13 species 10.6-23%). Blood analysis showed a 35 to 37% protein binding over a period of several hours.

Metabolism

Morphine is extensively metabolised by hepatic biotransformation and animal studies suggest a significant degree of metabolism in the intestine prior to absorption. The major mechanism of morphine biotransformation is conjugation with glucuronic acid (glucuronidation) to form both active and inactive products. This mechanism is so active that by 10-20 minutes after i.v. injection of morphine in dogs, the concentration of morphine metabolites in plasma exceeds that of unchanged morphine. While the relative contribution of the different routes of metabolism varies between oral and parenteral doses, there are no routes of metabolism specific to a particular mode of administration. Ratios do not seem to change with increasing doses or prolonged treatment. Morphine-3-glucuronide (M3G) is the major metabolite (approximately 45% of dose, with 1/10 of the morphine analgesic potency) while morphine-6-glucuronide (M6G) is a quantitatively minor (5% of dose) but active metabolite. M6G is approximately 40 times as active as morphine in suppressing nociceptive stimuli (hot plate test in rats) following intracerebral administration and therefore could be responsible for the prolonged narcosis. Other minor metabolites include normorphine (1-5% of dose) and normorphine-3-glucuronide (3% of dose), morphine-3,6-diglucuronide, morphine ethereal sulphate and normorphine glucuronides. Conversion of morphine to codeine by O-methylation has also been reported. Normorphine (NM) is also active, and is formed to a greater extent after oral administration; it is not, however, usually found in plasma. NM may be neurotoxic. Penetration of glucuronides through the blood-brain-barrier is restricted. However, the ratio of morphine metabolites to morphine in the brain is constantly increasing after morphine administration. M6G has been demonstrated to have the ability to penetrate the brain of rats. M6G is detected in CSF after systemic administration, although it cannot be formed in the central nervous system. M6G is believed, however, to cross the blood-brain-barrier and accumulate in CNS with repeated administration.

Excretion

Morphine and its metabolites are mainly excreted via urine and faeces. The mean elimination half-life for morphine in blood and plasma is 2.7 hours (range 1.2-4.9 hours) and 2.95 hours (range 1.8-5 hours), respectively. The mean blood and plasma clearance is 1.16 l/ minute (range 0.32-1.7 l/min) and 1.09 l/min (range 0.77-1.1 l/min), respectively. This high clearance value is approximately 75% of hepatic blood flow (HBF) and suggests that HBF rather than the capacity of the liver enzymes to metabolize morphine is the major determinant of morphine clearance. Morphine is eliminated from the CSF at a rate which is about five times slower than from plasma. Although renal excretion is a minor route of elimination for unchanged morphine, it constitutes the major mechanism of elimination of conjugated metabolites of morphine. The urinary free morphine accounts for less than 10% of an administered dose. It is eliminated mainly as M3G and M6G; 90% of total excretion takes place during the first day. The renal handling of morphine is a complex combination of glomerular filtration, active tubular secretion, and possibly active reabsorption. In a crossover study in sheep, the total body- and regional clearances of morphine were measured after i.v. application of a physiological dose (Sloan et al., 1991). The mean total body clearance of morphine was 1.63

l/min; this comprised 1.01 l/min clearance by the liver and 0.55 l/min by the kidneys. There was no evidence of dose-dependent clearance or significant extraction of morphine by lungs, brain, heart, gut or hindquarters. 12.3% of the administered dose was recovered as unmetabolised morphine from 48 hour urine collection. It was concluded that the liver and kidneys account for the majority of morphine clearance, and that the kidneys both excrete and metabolize morphine. The liver is one of the most important organs for morphine-clearance. Following formation in the liver, morphine-glucuronides undergo enterohepatic recirculation. In rodents there is an evidence that extensive enterohepatic circulation of morphine occurs and that up to 50% of an oral dose may be excreted in the bile. Conjugates excreted in bile gain access to the gut lumen, and hydrolysis to the parent drug will then result in reabsorption of intact morphine. The biliary excretion of morphine glucuronides and enterohepatic recycling of morphine resulting from the hydrolysis of glucuronides in the gastrointestinal tract could also explain the effect of the prolonged narcosis. Biliary excretion of morphine metabolites occurring with enterohepatic circulation of morphine ultimately results in faecal excretion of both morphine and its metabolites (5-10% of the dose). Further, enterohepatic circulation of morphine and its glucuronides accounts for small amount of morphine in the urine several days after the last dose. Horton & Pollack (1991) have shown that enterohepatic recirculation and renal metabolism contribute significantly to disposition of morphine and its glucuronide conjugate in rat. Approx. 15.8% of administered dose (2.5 mg/kg as an i.v. bolus) was subject to enterohepatic recirculation. Renal metabolic clearance was calculated as 15.7 ml/min/kg, accounting for 28.5% of morphine systemic clearance. Hepatic clearance of 31.4 ml/min/kg accounted for 56.8% of total systemic clearance.

III.3 Toxicology

Single dose toxicity

Acute toxicity has been investigated in a number of species, whereby observation periods for deaths were usually 24 hours. Death is usually caused by convulsions and respiratory spasm. Acute toxicity was determined in mice (taconic mice, n = 20, 20-30 g, 30-40 days old) by i.p. injections of morphine (as hydrochloride) in doses of 50, 100, 200, 400 mg/kg. Acute LD50 of 148 mg/kg was found (95 % confidence interval: 102-197). Animals were observed for 24 hours. Death followed a generalised convulsive state (Brailowsky et al., 1981). In another experiment, s.c. acute LD50 of 525 mg/kg was found (female CF-1 albino mice, n = 10/dose level, four doses between 400-700 mg/kg, 95% confidence interval: 500-551; given as sulphate, Harpel & Gautieri, 1968). I.v. LD50 was found to be 225mg/kg (n=24, as hydrochloride). General effects were excitation such as tail reaction, and with lethal doses general convulsions. Death was caused by respiratory spasm (Fromherz, 1951). Similar results have been found in another study with mice (Swiss Webster, female, n = 10, 16-23 g), with LD50 values of 670 mg/ kg after p.o., 200 mg/kg after i.v. and 334 mg/kg after i.m. administration of morphine sulphate (Kimura et al., 1971). According to other experiments in mice (male, n = 10/ group, 18-22 g), LD50 values after oral and s.c. administration (as sulphate) amounted to 600 mg/kg and 375 mg/kg, respectively (Witkin et al., 1961). Acute toxicity of morphine varies as a function of time. When morphine sulphate was injected s.c. in mice (male taconic mice, 15-30 g, n = 30 for each dose level, groups of five animals/time, ten/cage) at four doses (50-400 mg/kg) at different times of the day, maximal LD50 of 314.87 mg/kg was found during light period at eight, and minimal LD50 of 68.32 mg/kg during the dark. The latency for death and the number of deaths were recorded up to 4h following morphine administration

(Campos et al., 1983). In rats (Sprague-Dawley, male, n = 6, 130-210 g), LD50 values of 78 mg morphine/kg have been found after i.m. administration of morphine sulphate (Kimura et al., 1971). In another study, LD50 of 140 mg/kg after i.v. injection of the monohydrate was determined in rats by extrapolation (Wistar, of either sex, n = 5, 120-150 g, dose groups 40, 60, 80, 100, 120 mg morphine/kg, 24h observation (Jackson, 1952). Acute toxicity is increased by stress, such as placebo injection before injection of morphine, but also housing conditions. When rats (Wistar, male, 250-300 g) were aggregated in groups of six animals/cage, 20/24 animals died after i.p. injection of 45 mg morphine sulphate/kg, whereas none of 24 individually housed rats died. After i.p. injection of 15 mg morphine sulphate/kg, again none of 50 isolated rats died, whereas 3/36 rats which were grouped to six in a basket, and 12/14 rats grouped seven to basket died (Sklar & Zalmann, 1977). In rabbits, acute i.v. lethal dose (n = 10) was 135 mg morphine/kg, given as hydrochloride (Fromherz, 1951). After injection they slumped on their abdomen and stretched their limbs away; respiration became slower and of Cheyne-Stokes type. With sublethal doses convulsions were observed. Death was caused by respiratory standstill. The following table (table 1) gives a summary of the acute toxicity of morphine based on investigations in different animal species.

Table 1. Acute toxicity of Morphine in different animal species.

Species	n (sex)	morphine-salt	LD 50 (mg/kg body weight)			Ref. No.
			p.o.[1], i.p.[2]	s.c.	i.m.[3] , i.v.[4]	
mouse	10	HCl	148[2] (102-197)			5
	10	SO_4		525 (500-551)		26
	24	HCl			225[4]	17
	10 (f)	SO_4	670[1] (532-845)		334[3] (321-361) 200[4] (169-236)	36
	10 (m)	SO_4	600±44.0[1]	375±16.4		60
	-	H_2O	524 (420-642)	416 (327-543)	183[4] (162-219)	28
	10 (m)	SO_4		68.32[min] 314.87[max]		8
rat	20	HCl		300		17
	6(m)	SO_4			78 (42-147)[3]	36
	5(f/m)	H_2O			140[4]	33
rabbit	10	HCl			135[4]	17

Table 1: n: number of animals for each dosis-group;
(f/m): female/male;
values put in parentheses: 95% confidence interval
HCl: morphine hydrochloride trihydrate [$C_{17}H_{19}NO_3$, HCl, $3H_2O$] - 375.8 Dalton;
SO_4: morphine sulfate [$(C_{17}H_{19}NO_3.)_2.H_2SO_4.5H_2O$] - 758.8 Dalton;
H_2O: morphine hydrochloride monohydrate [$C_{17}H_{19}NO_3.HCl.H_2O$] - 303.4 Dalton;

Effects of morphine are somewhat different in different species. In mice, visible excitation and the tail reaction are first observed. In rats, a listless abdominal or lateral position is assumed, protrusion of the eyes is regularly observed. Rabbits react in a similar manner, extremities are spread listlessly, respiration is slowed and of Cheyne-Stoke type. Sublethal doses cause tetanic spasms and opisthotonus. In cats, strong stimulation of central nervous system is found, with signs of anxiety, maximal dilatation of pupils, salivation and occasionally vomit. At higher doses, tetanic convulsions occur. Death is usually caused by respiratory spasm or general convulsions.

Repeat-dose toxicity

When rats (male Sprague-Dawley, two groups of n = 15, 35 days old) received morphine sulphate (50 mg/kg/day, .s.c.) or sterile water (control group) over nine weeks, marked sedation with subsequent development of tolerance was observed during days one and two in the morphine group. At week seven to nine rats became aggressive and irritable, presumably as result of increasing morphine dependence. Morphine-treated rats showed overall 30% reduction of body weight gain (due to reduced food intake during the first three dosing weeks), reduced prostatic weights, decrease in spermatids and persistent reductions of luteinizing hormone (LH)- and testosterone serum concentrations compared with control group. Pituitary gonadotrophic cells showed atrophy, nuclear pyknosis and condensation of granules, indicative of reduced secretory activity. Effects were reversible after 13 weeks recovery. There were three premature deaths, attributable to chronic respiratory disease: two morphine-treated rats (during week nine of dosing, during four- week recovery period) and one control rat during week seven of 13-week recovery period (James et al., 1980). When immature, 21 day-old female rats were exposed to morphine sulphate (50 mg/kg i.p. for seven days) a significant reduction in the number of follicles undergoing growth was observed after 24 hours and after seven days (Lintern-Moore et al., 1979). Morphine alters therefore ovarian function in the rat and delays onset of puberty. Other problems of long term administration have not been documented, neither in animals nor in humans. However, adequate and well controlled studies in animals or humans have not been published. The following table (table 2) gives a summary of the repeated dose toxicity of morphine :

Table 2. Repeated dose toxicity of Morphine.

Species n (sex)	Dose (mg/kg/day		Duration of treatment/ morphine-salt	Results	Ref. No.
	s.c.	i.p.			
rat n=30 (m) 2 groups	50	-	9 weeks SO_4	3 premature deaths, attributable to chronic respiratory disease: 2 morphine-treated rats (during week 9 of dosing, during 4-week recovery period) and 1 control rat during week 7 of 13-week recovery period;	34
rat (immature) n=24 (f)	-	50	7 days SO_4	after 24 h and after 7 days a significant reduction in the number of follicles under-going growth was observed;	41
rat (pregnant.) n=131 (f) 4 groups	10 35 70 *)	-	15	70mg/kg/d was the highest dose without respiratory depression, or increased maternal mortality, or de-creased weight loss	18

Table 2: n: total number of animals; m: male; f: female
SO_4: morphine sulfate $[(C_{17}H_{19}NO_3.)_2.H_2SO_4.5H_2O]$ - 758.8 Dalton;

Genotoxicity

Direct testing of morphine on chromosomes of human leucocytes in culture gave negative results. Mice (Swiss, both sexes, aged 70-100 days, approx. 20 g, n = 5) receiving i.p. injections of morphine sulphate (single dose of 3.2 mg/kg or daily over seven days) showed a significant increase in the breakage frequency of chromosomes of bone-marrow cells compared with control mice receiving distilled water. Lowest breakage frequency was observed at 24 hours (nine times the control value) and highest after 16 hours (12 times the control). No dose dependency could be observed; all doses tested (3.2-64 mg/kg) led to an increase in breakage frequency approx. ten times the control value. Chromosomal aberrations and mutations have been observed also in plant material exposed to morphine (Swain et al., 1980). Morphine was not teratogenic but decreased pregnancy rate, growth and survival of the offspring. In experiments using chronically s.c. implanted osmotic minipumps morphine (or saline as control) was delivered in doses of 10, 35 or 70 mg/kg/day to timed-pregnant rats (Sprague-Dawley, 30 animals /group) from day five of gestation till day 19 when caesarean section was performed. In this way, plasma levels of approx. 200, 550 and 670 ng/ml could be achieved. Dose dependent decrease of pregnancy rate could be observed; (6% in the 70 mg-group, 57% in the 35 mg-, and 83% in the control group). There were no differences in the number of implantations, live foetuses, resorption rate, mean foetal weight, sex ratio, and percent of runts (foetuses weighing 25% less than the mean weight of their litter) among the control and 10 mg or 35 mg groups. No significant abnormalities were noted, apart from slightly enlarged cerebral ventricles and of generalised decreased ossification in the 35 mg group which is indicative of growth retardation. Mortality rate of the foetuses was significantly increased in the morphine group; most deaths occurred within the first two days after birth. Mean birth weight was also significantly lower than in control group on days seven and 28 after birth (Fujinaga & Mazze, 1988). In another study (Harpel & Gautieri, 1968), though congenital abnormalities were produced by morphine, the doses required were extremely high and quite close to the LD50 of 525 mg/kg in nongravid mice. It was concluded that the teratogenic potential of morphine is low.

Carcinogenicity

Morphine can enhance tumour growth and reduce survival time. Incubation of cell cultures with morphine has no effect on tumour cell growth. This suggests that effects are the result of an overall immunosuppressive effect. Morphine shows a number of effects on the immune system; few are thought to be direct, but rather mediated centrally followed by increased glucocorticoids, catecholamines, and stimulation of the sympathetic nervous system. When morphine pellets (8-, 25-, 75 mg or placebo) were implanted in mice, corticosterone increased in parallel with morphine. Weight of lymphoid organs, spleen and thymus, were significantly reduced. In contrast to increased serum proteins, C3 component of complement was reduced in a dose-dependent manner; lymphocytes and eosinophils were also reduced, and neutrophils increased; B-cells and T-cells were also decreased without changing their ratio. Natural killer cell activity was reduced, as was the phagocytic capacity of Kupffer cells. The most sensitive immune parameters included the T-cell dependent antibody response to sheep red blood cells, Kupffer cell phagocytosis, and serum complement levels displaying a dose-related suppression in response to morphine (LeVier et al., 1994). Morphine administration was accompanied by 30% decrease in the absolute number of lymphocytes circulating in peripheral blood in rat. *In vivo* administration of high doses of morphine to animals has been shown to suppress the cytotoxic activity of natural killer cells in rats and mice (Carpenter et al., 1994) and splenic T-cell mitogenic response. In mice, morphine drastically reduced reticuloendothelial system activity, phagocyte count, phagocytic index, killing properties, and superoxide anion production in polymorpho-nuclear leucocytes and macrophages. Similar effects on alveolar macrophage count, phagocytosis, and killing properties were found in rabbits.

Fertility and early embryonic development

Ahmadnia et al. (2016) studied the influence of chronic drug abuse on sex hormones and spermatogenesis in rats. Thirty 60-day-old male rats were divided into control and target groups. The target group underwent 5 mg/kg intraperitoneal injections of morphine twice a day while the control group underwent normal saline injections (at the same dosage). After 60 days, the rats were anesthetised, and after blood sampling, they underwent bilateral orchiepididymectomy. Histological and hormonal evaluations were performed on the samples. Levels of sex hormonal features and spermatogenesis were significantly reduced in the target group compared to the control group. LH levels showed a meaningful decrease in the target group, but follicle stimulating hormone (FSH) and testosterone levels did not. On histological section analysis, mature sperm were meaningfully decreased in the target group. Takzare et al. (2016) evaluated the addiction effects of morphine and its derivatives on rats spermatogenesis. Forty male Wistar rats were randomly divided into five equal groups, which were exposed either with intravenous morphine, naloxone, naloxone and morphine, sham (with normal saline injection) and a control group without infusion. Spermatogenesis was assessed after three months via histological sections with hematoxylin and eosin staining, using a light microscope based on measurement of spermatogonia, spermatocyte, spermatid, and spermatozoa. Those rats that received opioids had changes in spermatogeness function. The population of spermatogenesis cycle cells at spermatogonia, spermatocyte, spermatid, and spermatozoa stages was significantly decreased in those rats that received opioid in comparison to the control group ($p < 0.05$). Histological studies revealed that changes in different groups of opioid application might affect sperm formation. Sperm count in morphine

group was (0±0) and in naloxone group, naloxone+morphine, sham and control were 235±3.77, 220±3.81, 247.12±6.10 and 250±6.54, respectively ($p < 0.001$). The authors concluded that morphine could affect all spermatogenesis stages. Tang et al. (2015) explored the potential consequences of morphine exposure on uterine receptivity and implantation during early pregnancy in C57BL/6 female mice (eight weeks old). To examine the effect of morphine on blastocyst implantation *in vivo*, pregnant or pseudo pregnant mice received intraperitoneal injections of morphine (50 mg/kg body weight) and/or naloxone (1 mg/kg body weight) on days three to four. Implantation sites were visualised on the morning of day five. The authors demonstrated that opioid receptors were spatiotemporally expressed in the uterus during the peri-implantation period. Employing a pharmacological approach combined with embryo transfer experiments, the authors further observed that although systemic morphine treatment exerts no apparent adverse influence on preimplantation ovarian secretion of progesterone and oestrogen, this aberrant activation of opioid signalling by morphine induces impaired luminal epithelial differentiation, decreased stromal cell proliferation, and poor angiogenesis, and thus hampers uterine receptivity and embryo implantation. These novel findings add a new line of evidence to better understand the causes for obvious adverse effects of opioid abuse on pregnancy success in women.

Embryo- foetal development

Maternal morphine treatment retards not only the growth of young rats but impairs also brain development. In the following experiment, female rats (Sprague-Dawley, 180-200 g, 19 morphine treated, 12 controls) received morphine in a starting dose of 10 mg/kg i.p. After five days, they were mated with males and morphine dose was maintained till the second day of pregnancy. From day two to eight of gestation, they received 20 mg/kg, then, beginning on day nine, dosages were increased by increments of 2 mg/ kg every two days until a maximum of 40 mg/kg was attained. Rats were then maintained on 40 mg/kg injection for the remainder of the experiment. Drug treated females gained less weight than controls during gestation and the first two weeks lactation. They had also smaller litter size, a greater number of stillborns, and a considerable higher infant mortality. Pups exposed to morphine showed significant retardation in body growth, and had smaller brain and cerebellar weights (Zagon & Mc Laughlin, 1977). In another experiment, morphine exposure during adolescence led to a pronounced inhibition of number of indices of sexual maturation in male rats. Prepubescent male rats (25-27 days old, Sprague Dawley) were implanted with morphine- or placebo-pellets with sustained release of morphine for three to four weeks. Whereas one group of 10-20 animals was sacrificed at weekly intervals (week one to four, six and nine) through adulthood for assessment of reproductive endocrine function, a large group was bred with drug-naive primiparous females (85 days of age) eight weeks after morphine or placebo pellet implantation. During adolescence morphine caused reduced serum testosterone and luteinizing hormone levels, reduced weights of testes and seminal vesicles. Breeding with drug-naive females resulted in significantly smaller litters when compared to controls without any influence on percentages of pregnancies. Upon reaching adult-hood, male offspring of morphine treated males had significantly lower serum testosterone, luteinizing hormone levels and adrenal weights, but hypothalamic ß-endorphin levels were only insignificantly elevated. In female morphine derived offspring large increases in serum corticosterone and ß-endorphin levels in the hypothalamus were observed, but no differences in reproductive endocrine status. No gross developmental anomalies or birth defects were noted (Cicero et al., 1991). Effects of morphine exposure in utero on offspring was tested also in mice. After

mating with males, seven females receiving morphine (0.5 mg/ml in drinking water during pregnancy and during two weeks of nursing) had given spontaneous birth to a total of 20 mice (41 in the control group). Sex ratios were similar in the two groups of this first generation. At the age of 2.5 months, mice were tested for shock-elicited escape behaviour on day one and for morphine sensitivity on day two. Sensitised animals showed a smaller latent period and a larger tolerance in respect to the analgesic effect of morphine than controls, in addition to changed behaviour in stress situations (Zimmerberg et al., 1974). The effects of morphine on the hippocampal neurochemical profile and neurogenesis in the dentate gyrus of the hippocampus were evaluated in neonatal rats (Traudt et al., 2012). For that, rat pups were injected twice daily with 2 mg/kg morphine or normal saline from postnatal days three to seven. On postnatal day eight, the hippocampal neurochemical profile was determined using *in vivo* 1H-NMR spectroscopy. The mRNA and protein concentrations of specific analytes were measured in hippocampus, and cell division in dentate gyrus was assessed using bromodeoxyuridine. The concentrations of GABA, taurine, and myo-insotol were decreased, whereas concentrations of glutathione, phosphoethanolamine, and choline-containing compounds were increased in morphine exposed rats relative to control rats. Morphine decreased glutamic acid decarboxylase enzyme levels and myelin basic protein mRNA expression in the hippocampus. Bromodeoxyuridine labelling in the dentate gyrus was decreased by 60-70% in morphine exposed rats. These results suggest that recurrent morphine administration during brain development alters hippocampal structure.

Concluding on the presented toxicology literature: single dose toxicity studies have been performed with morphine in mouse, rat and rabbit, cat at very high doses to establish lethality. Such toxicity studies are not considered informative any more. Given the well-known pharmacological profile of morphine, and the extensive clinical experience which spans decades, acute effects of morphine have been adequately covered. However, clinical experience with morphine supersedes animal data. Chronic exposure to morphine has been assessed in rats. Most adverse effects could be attributed to the known pharmacological profile of morphine; marked sedation and development of tolerance. Because morphine is not intended for chronic use, and because clinical experience with morphine supersedes animal data, the provided overview is adequate. Literature suggests that morphine is potentially genotoxic, although the data is equivocal. However, no special hazard for humans is revealed in addition to what is known from clinical experience. Formal carcinogenicity studies have not been performed with morphine. Formal fertility studies were not conducted. In literature, morphine appears to reduce LH levels in male rats, and reduces total sperm count and spermatogenesis is decreased. Systemic morphine treatment exerts no apparent adverse influence on preimplantation ovarian secretion of progesterone and estrogen, this aberrant activation of opioid signalling by morphine induces impaired luminal epithelial differentiation, decreased stromal cell proliferation, and poor angiogenesis, and thus hampers uterine receptivity and embryo implantation. No formal reproductive toxicity studies have been completed. Maternal administration of morphine to rats results in decreased litter sizes, a greater number of still borns and higher infant mortality. Exposed pups had retarded growth and brain development. Structural brain changes have also been observed in mice. Exposure to morphine in juvenile male rats leads to inhibition of sexual maturation and decreased fertility parameters.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Assessment of the ERA to be included if ERA data have been submitted by the MAH.
A summary of the main studies should be provided by using the following table:

Summary of main study results

Substance (INN/Invented Name): Morphine					
CAS-number (if available): 57-27-2					
PBT screening		Result		Conclusion	
Bioaccumulation potential- log K_{ow}	OECD107 or …	P.M.		-	
PBT-assessment					
Parameter	**Result relevant for conclusion**			**Conclusion**	
Bioaccumulation	log K_{ow}	P.M.		-	
	BCF	P.M.		-	
Persistence	ready biodegradability	P.M.		-	
	DegT50	P.M.		-	
Toxicity	NOEC algae NOEC crustacea NOEC fish	P.M.		-	
	CMR	not investigated		potentially T	
PBT-statement :	P.M.				
Phase I					
Calculation	**Value**	**Unit**		**Conclusion**	
$PEC_{surfacewater}$, default	0.6	µg/L		> 0.01 threshold: Y	
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**		**Remarks**	
Adsorption-Desorption	OECD 106 or …	*P.M.*			
Ready Biodegradability Test	OECD 301…	P.M.			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	P.M.		Not required if readily biodegradable	
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	P.M.	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	P.M.	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	P.M.	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	P.M.	µg/L	

Conclusions on ERA

Initially, the PBT assessment couldn't be concluded as a report or publication with which the reliability of the log K_{ow} can be assessed was absent. Furthermore, the PEC_{sw} is higher than 0.01 µg/L a phase II assessment is required and should be submitted by the MAH.

However, considering that morphine has been widely used since the 19th century and the current application will replace an existing market share, no increase in the use of morphine in the Netherlands is expected. Therefore, further studies are not needed.

III.5 Discussion on the non-clinical aspects

The submission is intended for well-established use. As such, the MAH has not provided additional non-clinical studies and further studies are not required. An overview based on literature review is, thus, appropriate. The effects of morphine are well known, and the literature on pharmacology, pharmacokinetics and toxicology has been adequately reviewed in the MAH's non-clinical overview.

IV. CLINICAL ASPECTS

IV.1 Introduction

Morphine hydrochloride trihydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

As Morfine HCL Focus is intended as a well-established use medicinal product, the MAH has submitted a literature review encompassing the pharmacokinetics, where pharmacokinetic data of Morfine HCL Focus was bridged to studies using morphine hydrochloride/sulphate formulations. Pharmacodynamics, clinical efficacy and safety have also been linked to clinical studies and are considered to be adequate.

Bridging effectiveness and safety of different morphine pharmacological formulations
Morphine was first isolated in 1804 by both Seguin and Courtois, but it was the German pharmacist Sertürner who first published its results in 1805. Morphine is an extremely well-studied molecule and numerous articles exist on the use of this well-established product. As is the case with many well-established use products, the details of the formulation cited in the literature is often omitted from the articles. All articles referenced in the clinical overview, were systematically searched and no formulations were specifically reported in any of the articles. However, the use of either the sulphate or hydrochloride salt form were reported within certain literature. Therefore, in the absence of such information, it is only feasible to establish links with formulations already licensed and available within the EU.

The product literature presented on the webpages of certain competent authorities such as the MEB, MHRA and SUKL were searched and a list of products commercially available in the EU with the same strength and pharmaceutical form as the proposed product was generated. The results are presented in chronological order in table 3.

Table 3. List of morphine solutions for injections (10 mg/ml) authorised in the EU in ampoules and vials.

Country of authorisation	Product name	MAH, MA No. & procedure	Year of licence	Active	Excipients
UK, IE and MT	Morphine sulphate 10 mg/ml solution for injection	AS Kalceks PL 47015/0003 UK/H/6752/001-003/DC	Oct 2018	Morphine sulphate	Sodium chloride HCl Water for injections
NL	Sendolor 10 mg/ml, oplossing voor injectie	Eurocept International BV RVG 121829	Sept 2017	Morphine hydrochloride.	Sodium chloride Water for injections
SE, NL, PL, CZ, PT, SL, ES	Morfine Kalceks 10 mg/ml, oplossing voor injectie	Kalceks RVG 119554	Dec 2016	Morphine hydrochloride.	HCl (for pH adjustment) Water for injection
UK	Morphine Sulfate 10mg/ml Solution for Injection	Wockhardt UK Ltd PL 29831/0146	Nov 1999	Morphine sulphate	Water for injections Sodium. metabisulfite Sodium hydroxide Hydrochloric acid
NL	Morfine HCl CF 10 mg/ml, oplossing voor injectie	Centrafarm B.V. RVG 50836	Dec 1992	Morphine hydrochloride.	Sodium chloride HCL Water for injection Nitrogen (head space)
NL	Morfine HCl Teva 10 mg/ml, oplossing voor injectie	Teva B.V. RVG 51950	Dec 1992	Morphine hydrochloride.	Sodium chloride Water for injection
CZ	MORPHIN Biotika 1% injekční roztok	BB Pharma, a.s. 65/780/92-S/C National	Dec 1992	Morphine hydrochloride.	Sodium chloride Glycine Disodium edetate dihydrate Water for injection Hydrochloric acid 35% (to adjust pH).
UK	Morphine Sulfate 1mg in 1mL Solution for Injection.	Torbay and South Devon NHS Foundation Trust PL 13079/0001	16/06/1998	Morphine sulphate	Sodium chloride Water for injections
UK	Morphine Sulfate 10mg in 1ml Solution for Injection	Macarthys Laboratories Ltd t/a Martindale Pharma, PL 01883/6138R	Jan 1982	Morphine sulphate	Sodium Chloride, Sodium Metabisulfite(E223) Water for Injection. The pH may be adjusted with Sodium Hydroxide or Sulfuric Acid Solution

As can be seen from table 3 these marketed products date as far back as 1982 and are fairly similar in their formulation. Each of the formulations listed in table 3 utilise water for injection as the main solvent and also most of the products use a pH adjuster. This is to be expected as the salts of morphine, such as hydrochloride and sulphate, are around 300 times more water soluble than the parent molecule and therefore easily forms an aqueous solution with water.

As these salts are much more acidic (with a pH around 5) than the saturated morphine hydrate solution which has a pH of 8.5, the pH of the final formulation often requires neutralizing with small amounts of sodium hydroxide and/or hydrochloric acid to make them suitable for injection.

The three products highlighted in grey contain additional excipients largely to stabilise and prolong the shelf-life of the product. The two UK products for example, contain the additional excipient sodium metabisulfite, whilst the Czech product "MORPHIN Biotika 1% injekční roztok" contains a solubilising agent (glycine) and a chelating agent (disodium edetate dihydrate). These examples demonstrate that a range of products already co-exist on the market.

The proposed composition of the ampoule and vial formulation are outlined in table 4 and 5 respectively. The ampoule formulation is completely in line with recently approved formulations marketed in the EU. Regarding the proposed vial presentation, this contains the additional excipients disodium edetate and citric acid. The disodium edetate is contained within the Czech formulation. In addition, disodium edetate is widely used in other parenteral formulations which is also acknowledged in the handbook of pharmaceutical excipients. Examples include, palonosetron 250 micrograms solution for injection (PL 20117/0295), Flumazenil 0.1 mg/ml solution for injection / infusion (UK/H/6055/001/DC), Dexamethasone 3.3 mg/ml solution for injection (PL 01502/0079. Disodium edetate is used as a chelating agent and is generally considered to be safe (Ref handbook of pharmaceutical excipients). It also listed in the food and drug authority (FDA)'s Inactive Ingredient Database and the Canadian List of Acceptable Non-medicinal Ingredients. Regarding the citric acid component this is primarily used as a buffering agent to maintain the pH of the solution and is widely used in parenteral formulations. In terms of safety it is included in the FDA Inactive Ingredients Database (for parenterals) and the Canadian List of Acceptable Non-medicinal Ingredients. It is also included in nonparenteral and parenteral medicines licensed in Japan and the UK.

Table 4. Composition of the proposed formulation in the ampoule presentation.

Ingredients	Composition [mg/ml]	Function	Monograph
Morphine HCl trihydrate	10.00	active drug substance	Ph.Eur.
Hydrochloric acid	0.00 to 0.12 *	pH adjuster	Ph.Eur.
Sodium hydroxide	0.00 to 0.04 *	pH adjuster	Ph.Eur.
Water for injections	ad 1.0 ml	solvent	Ph.Eur.
Nitrogen	---	air displace agent	Ph.Eur.

* q.s. to pH 2.9 – 3.1

Table 5. Composition of the proposed formulation in the vial presentation.

Name of ingredients	Composition mg per ml	Unit formula mg per 10 ml (for 100 mg vial)	Unit formula mg per 10 ml (for 200mg vial)	Function	Reference to standards
Morphine hydrochloride	10.0/20.0 mg	100mg	200 mg	API	Ph.Eur.
Citric acid monohydrate	0.5 mg	5 mg	5 mg	Buffering agent Chelating agent	Ph.Eur.
Disodium edetate	0.1 mg	1 mg	1 mg	Chelating agent	Ph.Eur.
Hydrochloric acid *	0 to 0.3 mg	0 to 3.0 mg	0 to 3.0 mg	pH adjusting agent	Ph.Eur.
Sodium hydroxide *	0 to 0.08 mg	0 to 0.08 mg	0 to 0.08 mg	pH adjusting agent	Ph.Eur.
Water for injections	ad 1 ml	ad 10 ml	ad 10 ml	Solvent	Ph.Eur.
Nitrogen	purging of the bulk solution, air replacement of head space of the vials				Ph.Eur.

* as diluted Hydrochloric acid or diluted Sodium hydroxide solution for pH adjustment, only added if necessary, to obtain the specified pH value of 3.0.

The pH and tonicity should be restricted to a range that mimics the physiological values (pH 7 to 8, buffer (1-10 mM) (Lee, Y.C., et al. International Journal of Pharmaceutics 253 (2003) 111–119) so that the formulation does not hurt on administration, therefore the use of sodium hydroxide/hydrochloric acid and citric acid (vial presentation only) has been used in the formulation to achieve this. Also, the pH range for the proposed product (pH 2.9-3.1) fits within the general range of the approved EU products which is specified to be lower than pH 4.0 but with varying lower limits ranging from no limit specified to pH 3.0. The solvent (water for injection), is purely used as a vehicle to deliver the active substance as an injectable and is commonly used for the delivery of injectables. The nitrogen component is completely inert and is used to fill the headspace to reduce any potential oxidative degradation and is commonly used for aqueous injectable formulations.
It has also been confirmed that each of the excipients used in the proposed formulation is in compliance with the Ph. Eur. and are common excipients used particularly in the formulation of injectables, with no known interactions with the drug substance.

Regarding the behaviour of the product, the formulation is relatively simple, and in line with other parenteral formulations on the market. The excipients are highly unlikely to have an impact on the safety and efficacy of the product. The fact that the pharmaceutical form is an aqueous parenteral it bypasses the gastrointestinal system and is therefore 100% bioavailable on administration.
Moreover, according to CHMP guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), it specifically states the following for parenteral solutions:

- Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the drug substance (e.g. complex formation), or otherwise affect the disposition of the drug substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any

difference in quantity does not affect the pharmacokinetics of the active substance.

- In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required.
- A bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on the viscosity.

Categorically it can be concluded that the proposed products fulfil the above criteria, as they contain comparable excipients to those listed in table 3. Also, the excipients will not have an impact on the viscosity as they are either soluble in water or are aqueous solutions themselves.

A broad range of morphine solutions for injection have been referred in the literature data. Both sulphate and HCl salts exists and both salts are highly soluble. In NL the registered solutions for injection contain morphine HCl trihydrate, as does the proposed formulation.
The proposed formulation does not contain critical excipients which may affect absorption and/or distribution. As correctly referred by the MAH, bioequivalence studies are not required in such cases, as the proposed formulation is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.
Bridging has been sufficiently supported.

IV.2 Pharmacodynamics

Opioid drugs act in both the central and peripheral nervous systems. Within the central nervous system, opioids have effects in many areas, including the spinal cord. Major advances have been made in understanding the mechanism of action of the opioids. The most important recent advances have been increased knowledge of the cellular action of opioids and identification of the sites of action of opioids in the brain.

Mechanism of action
Opioid receptors are localised in various parts of the nociceptive system: in the gelatinous matter, in the raphe nuclei of the medulla oblongata, in the periaqueductal gray matter, and the medial thalamic nuclei. The receptors are also present in parts of the brain that control the motor sphere, behaviour and mood, or that take part in the neuro-endocrine system. There is evidence that opiate effects and side effects may also be initiated by activation of opiate receptors located outside the CNS. Outside the CNS, opioid receptors can be found predominantly in the small intestine (regulation of the intestinal motility), but also in other organs.

Primary and secondary pharmacology
The nociceptive system is accompanied by the antinociceptive system via opioid receptors. Opioid receptors are localised in various parts of the nociceptive system: in the gelatinous matter, in the raphe nuclei of the medulla oblongata, in the periaqueductal gray matter, and

the medial thalamic nuclei. The receptors are also present in parts of the brain that control the motor sphere, behaviour and mood, or that take part in the neuro-endocrine system. There is evidence that opiate effects and side effects may also be initiated by activation of opiate receptors located outside the CNS. Outside the CNS, opioid receptors can be found predominantly in the small intestine (regulation of the intestinal motility), but also in other organs (Jurna, 1992; Snyder, 1977; Goodman and Gilman's 10th Ed., 2001). Multiple opioid receptors and subtypes have been identified and classified. In the central nervous system there are four primary opioid receptor types. The μ-receptor is the binding site for the phencyclidines. Opiate antagonists such as naloxone do not inhibit all effects mediated through this receptor, and consequently it is not regarded as an opioid receptor. Morphine mainly acts through the μ-receptors. The μ-receptor for morphine is subdivided into μ-1 (supra spinal and spinal analgesia, euphoria) and μ-2 (respiratory depression, inhibition of gastrointestinal motility). The morphine-dependent analgesia is due to interactions of morphine on various sites of action in the CNS; amongst others, morphine has an influence on the system of the neurotransmitters. A linkage of morphine to the opioid receptor (μ-receptor) of the terminal axons of afferent fibres in the gelatinous matter reduces the release of neurotransmitters, such as the substance P, which take part in conducting pain impulses (Schechter et al., 1993; Chrubasik & Chrubasik, 1995). The major use of opiates is to provide analgesia. They may also be used to achieve sedation, to suppress coughs and as anti-diarrhoeal agent (Sjögren & Eriksen, 1994). Pharmacodynamic action of morphine includes analgesia, euphoria, respiratory depression, depression of cough reflex, nausea and vomiting, pupillary constriction, increase in tone and reduced motility in many parts of the gastrointestinal system, histamine release inducing bronchoconstriction, hypotension, urticaria and itching.

Relationship between plasma concentration and effect

Pain is characterised by its multi-dimensional nature, explaining in part why the pharmacokinetic /pharmacodynamic (PK/PD) relationships are not straightforward for analgesics (Lorenzini et al., 2012). Several studies have attempted to assess the PK and PD of morphine and M6G in healthy human volunteers. The analgesic effects of morphine and M6G as well as the PK/PD relationship were evaluated in a cross-over study assessing thermal pain in 8 healthy volunteers. These volunteers received a 10 mg 5-min morphine intravenous infusion (Murthy et al., 2002). The fractional contribution of M6G to analgesia ranged from 0.1 to 66%. The above mentioned contribution appeared to differ between men and women. A mean contribution of 32 ± 19%(mean ± S.E.M.) in men (n = 3) and 13 ± 8% in women was observed. As the overall response to morphine increased, the fractional contribution of M6G to analgesia declined. An indirect response effect-compartment model was used, which assumed a linear relationship between the thermal pain threshold and the effect-site concentration. The mean equilibration rate constant (ke0) value was 4.43/hour.

The sex difference in morphine analgesia has also been observed in another study (Sarton et al., 2000). This study was performed in ten healthy male and ten healthy female volunteers. These volunteers were administered a 100 μg/kg i.v. bolus of morphine followed by a one-hour 30 μg/kg/hour infusion. The pain detection and tolerance thresholds to a transcutaneous electrical stimulation were used to assess the anti-nociceptive effect of morphine. An effect compartment model was postulated. A significant difference between the men and women was observed for the parameters ke0 and half-maximal activity concentration (AC50). This is

the effect-site concentration causing 50% attenuation in an inhibitory sigmoid maximal effect (E_{max}) model. The blood-effect site equilibration half-life t1/2ke0 was 1.6 and 3.8 hours for pain detection threshold, and 1.6 and 4.8 hours for the pain tolerance threshold in men and women, respectively. The concentrations of AC50 were 71.2 and 41.7 nM for the pain detection threshold in men and women, respectively. The concentrations of AC50 were 76.5and 32.9 nM for pain tolerance threshold in men and women, respectively. The observed sex differences in effect were unrelated to pharmacokinetic differences. The results suggested that morphine had a greater potency but showed a slower speed of onset and offset of analgesia in women. This difference does not appear because of the metabolite M6G, as shown by a study performed by the same research group, which used the same experimental transcutaneous model of pain (Romberg et al., 2004). In this cross-over, placebo-controlled study, ten healthy male and healthy female volunteers received either M6G (0.3 mg/kg) or placebo. M6G produced a greater analgesia than placebo. However, a sex-dependent effect could not be detected. A large inter-individual variability as expressed by the coefficient of variation (CV) was observed for t1/2ke0 (CV = 218%) and C25 (CV =167%), which is the effect-site M6G concentration causing a 25% increase in current for pain tolerance. The t1/2ke0 was 6.2 hours, thereby suggesting a long delay between the time course of plasma concentration and the time-course of analgesic effects. The above mentioned delay could be explained by a slower penetration of the blood-brain barrier by M6G when compared with morphine, which could be due to its more hydrophilic nature or its interaction with some transporters.

Skarke et al. (2003) further confirmed this difference of delay between morphine and M6G. In the study, 12 healthy volunteers received morphine (26-66 mg), M6G (63-112 mg) or placebo as an i.v. bolus, in a cross-over design. This was followed by infusion during 1.8-6.4 hours. Morphine and M6G significantly increased the pain tolerance to electrical stimulation when compared with placebo, but not the pain detection threshold. No difference was observed between morphine and M6G. The t1/2ke0 was 2.6 and 8.2 hours for morphine and M6G, respectively. Pain tolerance was linearly related to the effect-site concentrations. The concentration-effect relationship was flatter for M6G than for morphine, as expressed by a lower value of the slope (0.05% versus 0.6% of increase in pain tolerance per nM of opioid at the effect site). In other words, a concentration of 1114 nM of M6G was required to increase the pain tolerance of 50%, as compared with 85 nM of morphine. The amount of M6G required to achieve the analgesic effect when compared with morphine was estimated to be about 25 times higher than the M6G formed from morphine. Thus, the above-mentioned observation suggests a small contribution of M6G to the observed short-term central opioid effects of morphine in normal conditions. However, with a long-term morphine treatment, it is possible that M6G accumulates and could reach sufficient concentrations to contribute more significantly to the analgesic effects of morphine.

Staahl et al. (2008) compared the PK/PD relationship of morphine and oxycodone in a multimodal experimental pain model, which implied both visceral and somatic experimental pain, measured in the oesophagus and on the skin, respectively. This cross-over study in 24 healthy volunteers (12 men, 12 women) showed a linear concentration-effect relationship for morphine, with an effect-compartment link. The t1/2ke0 for somatic pain was 23 and 43 minutes. for thermal and electrical-induced pain, respectively. The t1/2ke0 for visceral pain was 433 and 24minutes. for mechanical and electrical stimulation, respectively. A greater variability was observed for visceral pain, thereby making modelling more difficult.

Pharmacodynamic interactions with other medicinal products or substances

The SmPC contents the most important observed interactions of morphine with other active substances. (Arzneimittelkursbuch, 2002/2003).

This document has been harmonised and aligned with the approved SmPC for "Morfine HCl Centrafarm 10 mg/ml". In the following table, some other possible drug interactions are summarised. (Arzneimittelkurs- buch, 2002/2003)

Table 6: Interactions of morphine with other substances

Interaction with	**Possible consequence**
alcohol, anaesthetics, analgesics, barbiturates	increased sedative action on the CNS
atropine	reduced toxicity of morphine (decreased resp. depression)
benzodiazepines, chlormezanone, isoniazid	increased action of morphine, sedation, respiratory depression
cimetidine	respiratory standstill, convulsions, confusion
clindamycin	gastrointestinal disorders(deterioration)
cumarin-anticoagulants	increased action of anticoagulants
hypnotics	increased sedative action on the CNS
levallorphan, nalorphine, naloxone-HCl	reduced action of morphine
levodopa	reduced action of levodopa
MAO-A inhibitors	narco-analgesic action increased
methysergide	reduced action of morphine
papaverine	reduced action of papaverine
phenothiazine	decrease in blood pressure, increased sedative action on the CNS
reserpine	reduced action of morphine
sedatives	increased sedative action on the CNS
saluretics	orthostatic hypotonia, reduced action of saluretics
suxamethonium chloride	bradycardia
tranquilizers, tricyclic antidepressants	increased sedative action on the CNS
zaleplon	drug dependence increased, euphoria increased

Interactions associated with opioid analgesics

Potent enzyme inducer rifampicin can reduce the serum concentration of morphine and decrease its analgesic effect; induction of the enzymes responsible for conversion of morphine to the active glucuronide metabolite did not seem to occur (Martindale, 2019).

An additive sedative effect is to be expected between opioid analgesics and benzodiazepines and has been reported with morphine and midazolam (Martindale, 2019). Concomitant use of opiate agonists and benzodiazepines or other CNS depressants including other opiate

agonists, anxiolytics, general anaesthetics, tranquilizers, sedatives, hypnotics, muscle relaxants, antipsychotics, and alcohol can increase the risk of respiratory depression, hypotension, profound sedation, coma, and death. Opiate analgesics frequently are implicated as contributing to fatal overdoses involving other CNS depressants, and epidemiologic studies have shown that a substantial proportion of fatal opiate overdoses involve the concurrent use of benzodiazepines, alcohol, or other CNS depressants (AHFS, 2019).
Opiate agonists may potentiate the effects of tricyclic antidepressants and monoamine oxidase (MAO) inhibitors, including procarbazine hydrochloride; therefore, opiate agonists should be used with great caution and in reduced dosage when used in conjunction with such drugs. Virtually all the reported incidents of opiate agonist interaction with MAO inhibitors have occurred in patients receiving meperidine (AHFS, 2019). Both clomipramine and amitriptyline significantly increased the plasma availability of morphine when given to cancer patients taking oral morphine solution. It was noted however that the potentiation of the analgesic effects of morphine by these drugs might not be confined to increased bioavailability of morphine; the dose of tricyclic to use with morphine in the treatment of cancer pain should be decided by clinical evaluation rather than by pharmacokinetic data (Martindale, 2019).
The effects of metoclopramide on morphine have included an antagonism of the effects of morphine on gastric emptying by intravenous metoclopramide (McNeill MJ, 1990).
Interactions between opioid analgesics and HIV-protease inhibitors or reverse transcriptase inhibitors are complex, and the results of the limited number of studies and reports *in vivo* have not always borne out predictions about the nature of potential interactions. Ritonavir is predicted to reduce plasma concentrations of morphine (Martindale, 2019).
Withdrawal symptoms may occur in patients receiving opiate agonists concomitantly with opiate antagonists (e.g., naloxone, naltrexone) or opiate partial agonists (e.g., buprenorphine, butorphanol, nalbuphine, pentazocine). Partial agonists should not be administered in patients receiving opiate agonists as they may reduce the analgesic effect and/or precipitate withdrawal symptoms (AHFS, 2019). Opiate agonists may cause severe hypotension in patients whose ability to maintain blood pressure has been compromised by blood volume depletion or concomitant use of certain drugs (e.g., general anesthetics, phenothiazines) (AHFS, 2019). Morphine may interact with warfarin and other coumarin anticoagulants and beta-adrenergic receptor blocking agents (Monograph, 2018).

IV.3 Clinical efficacy

The MAH provided a clinical efficacy report based on (number) literary references, a description of these can be found below:
Malignant growth:

- Harris et al., 2003. This was a prospective, randomised clinical trial (RCT) with a total of 62 patients. Comparing i.v with oral administration, total pain relief reported by patient was the primary outcome. Treatment consisted of: i.v. group - 1.5 mg every ten minutes till complete pain relief or severe side effects, oral treatment - 5 or 10 mg per 4 h. Outcomes of this study were: after 1 h: 27/31 had total pain relief in i.v. group and 8/31 in oral treatment group, after 24 h: 22/31 i.v. and 25/31 oral treatment group, after 48 h: 22/31 i.v. & 26/31 oral.

- Elsner et al., 2005. This was an open RCT with a total of 39 patients. s.c, versus i.v. was compared, using a tool to measure visual analogue scale (VAS) pain. Treatment consisted of: i.v. group - 2-5 mg every 5 minutes. s.c. group - 10-40mg every 30 minutes. Outcomes of this study were: 77% reported at least sufficient pain reduction, mean VAS decreased from 83 to 32 (i.v) and from 68 to 42 (s.c).
- Corli et al., 2016. This was a four-armed study with a total of 520 patients comparing oral morphine, oral oxycodone, transdermal (TD) fentanyl and TD buprenorphine in a 1 : 1 : 1 : 1 ratio. 28 days follow up, measured by worst pain indication (WPI), and average pain intensity (API). Treatment consisted of morphine (mg/day) baseline doses (BD) standard deviation (SD): 45.7 (16.2) final doses mean (FD) 58.9 (38.6), oxycodone: BD (SD): 44.6 (16) FD 71.1 (60.8), buprenorphine BD (SD): 53.7 (12.5) FD 80.1 (40.4) and TD fentanyl BD (SD): 53.4 (14.2) FD 111.4 (74.9). Outcomes of this study were: WPI & API decreased over four weeks which was comparable between groups. NRs 13.9% (morphine), 17.6% (oxycodone), 9.4% (buprenorphine), 13.7% (fentanyl).

Postoperative pain

- Study Code: FIWI.doc/24.11.1994. This was an open trial with a total of 20 female patients suffering from postoperative pain due to vaginal and abdominal surgery. This study aimed to investigate the efficacy of 200 mg/10 ml Morphine HCl.3H2O in this setting. Treatment consisted of a step-by-step titration of morphine (2 mg bolus) with an overall morphine dose of 46-120 mg. Outcomes of this study were: 5/20 pain free immediately after surgery, 17/20 completely pain free within 36 h.
- Study Code: No.: ILIAS01.XLS. This study with a total of 50 patients with postoperative pain or pain due to malignant growth compared the epidural (e.d), i.v, s.c, i.t, and i.m administration in a 1:1:1:1:1 ratio, using a tool to measure VAS pain. Treatment consisted of 2.9 mg e.d, 110.9 mg i.v, 113.0 mg s.c, 35.0 mg i.m and 1.0 mg intrathecal morphine (ITM). Outcomes of this study were: average VAS-score changes from baseline to 96 hours i.v (-1.7), s.c (-1.4),i.m (-2.1),ITM (-1.3) and e.d (-1.7).
- Reinoso-Barbero et al., 2001. This was a prospective, double-blind trial with 15 children (2 – 16 years old). Treatment consisted of morphine bolus of 20 µg/kg in 0.5 ml/kg saline every eight hours. Outcome of this study was: resting pain score (RPS)<4 in 87% of patients.
- Correll et al.,2001. This was a prospectively, randomised trial with 18 patients who had received a major surgical procedure. This study aimed to compare e.d. analgesia or patient-controlled analgesia (PCA). Treatment consisted of 2 mg of preservative-free morphine via the e.d. catheter. Outcomes of this study were: e.d.-final VAS= 0, PCA-final VAS= 10. The total length of hospitalization (101 vs. 126 days).
- Urban et al., 2002. This was a RCT with a total of 65 patients who received elective

posterior spinal fusions, a tool to measure VAS pain was used. Treatment consisted of spinal morphine as follows: 10 µg/kg, 20 µg/kg, or none. Outcomes of this study were: VAS-arrival Post Anesthesia Care Unit control (2.7), 10 µg/kg (1.6), 20 µg/kg (0.8).

- Kong et al., 2002. This was a prospective RCT with a total of 35 patients who received laparoscopic colorectal surgery. Treatment consisted of ITM + local anaesthetic (LA); bupivacaine + 0.2 mg ITM. LA; bupivacaine + 1 ml normal saline. Outcomes of this study were: 18 mg reduction PCA morphine. ITM group. Moderate to severe pain in PCA group, 0 in ITM group.
- Devys et al., 2003. This was a study with a total of 60 patients who had received major abdominal surgery that aimed to compare PCA with morphine to the combined use of ITM and PCA. Treatment consisted of Intrathecal morphine (0.3 or 0.4 mg) before induction of general anaesthesia. Outcomes of this study were: morphine consumption reduction (MCR) = 9 vs. 40 mg mean consumption for ITM+PCA and PCA alone groups.
- Boulanger et al.,2002. This was a randomised, partly-blinded study with a total of 62 patients undergoing elective cardiac surgery that aimed to compare the use of ITM, ITP or s.c. during these surgical procedures. Treatment consisted of ITM: 0.02 mg/kg to 1 mg/kg s.c.. Intrathecal placebo (ITP) Outcomes of this study were the amounts of i.v. morphine required after surgery: 3.2 mg in ITM group, 7mg ITP, 6.5 mg s.c.
- Wu et al., 2002. This was a RCT, crossover study with a total of 32 patients after limb amputations that aimed to compare i.v. morphine v.s lidocaine and measured subjects' self-reported pain relief. Treatment consisted of morphine (mg/kg): 0.05 bolus + 0.2 infusion or lidocaine (mg/kg): one bolus + four infusions. Outcomes of this study were: 45-48% pain relief in morphine group, 26-33% in lidocaine group and 3-8% in placebo group.
- Terajima et al., 2003. This was a RCT study with a total of 45 patients who received a c-section and aimed to compare spinal anaesthesia bupivacaine with/without intrathecal morphine. Treatment consisted of bupivacaine 10 mg and/or ITM 0.2 mg. Outcomes of this study were: with vs without ITM: time to first request for additional analgesia (hours) 8.3 v.s 24, requested analgesics within 24 hours 90% v.s 0%.
- Duale et al., 2003. This was a prospective, randomised, double-blind trial with a total of 53 patients who received an elective c-section and aimed to compare the efficacy of e.d. and IT morphine. Treatment consisted of 2 mg e.d morphine + 1 ml IT normal saline or 0.075 mg of ITM + 2 ml e.d. normal saline. Outcomes of this study were: e.d. vs ITM: time to first demand of morphine (307.5 v.s 310 min), additional morphine consumption (AMC) (4 vs 1.5 mg).
- Rathmell et al., 2003. This was a randomised trial with a total of 80 patients after

hip and knee arthroplasty and aimed to compare the efficacy and safety of intrathecal morphine in different doses. Treatment consisted of 0.0, 0.1, 0.2, or 0.3 mg IT morphine. Outcomes of this study were: 0.1, 0.2, or 0.3 mg ITMs v.s. controls: hip arthroplasty, AMC (mg) after 24 hrs : 34.4, 22.3, 30.6 v.s 76.9, knee arthroplasty: 58, 47.1, 68.6 v.s. 40.

- Raj et al.,2004. This was a randomised double-blind study with a total of 40 adults undergoing knee arthroscopy and aimed to compare the effects of intra-articular (IAM) vs. i.m morphine for 24-hours post injection. Treatment consisted of 10 mg IAM vs. 10 mg i.m injection. Outcomes of this study were: IAM v.s i.m VAS: (mean 18 vs. 34).
- Habib et al., 2005. This was a prospective case-control study with a total of 57 women undergoing postpartum bilateral tubal ligation. Treatment consisted of spinal analgesia; 12.75 mg bupivacaine + 20 µg fentanyl, + 50 µg morphine sulfate or 0.05 ml preservative-free saline. Outcomes of this study were: VAS in morphine group was less at rest (P=0.008) and on movement (P<0.0001) Rescue analgesia use was: (2 vs 4) (P < 0.006).
- Bowrey et al., 2005. This was a randomised double-blind study with a total of 70 patients undergoing knee replacement surgery and aimed to compare the efficacy and side-effect profile of 0.2 mg and 0.5 mg ITM. Treatment consisted of 0.2 mg and 0.5 mg ITM. Outcomes of this study were: 0.5 vs 0.2 mg group : required rescue analgesia during the first 24 hours 48% vs. 85%, (p = 0.003).consumption of the rescue analgesic 0 vs. 100 mg,(p = 0.02).
- Bae et al., 2017. This was a randomised study with a total of 30 patients undergoing robot-assisted laparoscopic prostatectomy (RALP) which aimed to compare numerical pain scores (NPSs) in postoperative patients 300 µg ITM with PCA vs 15 patients only PCA use. The treatment consisted of 300 µg morphine just in the ITM group. Outcomes of this study were: ITM vs PCA: NPSs on coughing 20 vs 60 at 24 hours (p = 0.001). morphine consumption at postoperative 24 hours 5 vs 17 mg, p = 0.001.
- El Sherif et al., 2016. This was a RCT study with a total of 100 morbidly obese patients with postoperative pain after laparoscopic bariatric surgery. Treatment consisted of 0.3 mg ITM added to bupivacaine 0.5% vs 0.3 mL i.t. saline added to bupivacaine. Outcomes from this study were: VAS lower in ITM during the immediate (p = 0.000), 30 minutes (p = 0.001) and 1 h (p = 0.016)

<u>Study regarding gender differences</u>

One abstract in this regard has been provided. 88 patients who underwent total abdominal hysterectomy or prostatectomy were enrolled in a randomised, double-blind, parallel-group, multi-centre study. Thirty-seven patients received a single dose of 7.5 mg morphine sulfate and 51 patients received placebo, both administered intravenously for one minute. Compared with baseline, morphine significantly reduced pain intensity at two, five, and ten minutes after administration. Patients receiving morphine reported mild pain relief at two and five minutes

after administration. Peak analgesic effects were reported two minutes after administration in 75% of the patients. Significant gender differences were also observed. In women, no significant differences in pain intensity were seen at any time between morphine and the control groups, whereas in men receiving morphine, pain intensity was significantly less at two, five, and ten minutes after administration compared to baseline and to placebo. Women were generally more satisfied with their pain treatment then were men (Larijani et al., 2004).

Clinical efficacy in children and neonates

Initially, the MAH submitted seven literary references to clinical trials. These references are shortly described below:

- Lynn et al., 2003. This study involved 20 < 3 months of age cyanotic and acyanotic infants and aimed to investigate i.v. morphine following thoracotomy. Treatment consisted of infusion 0.28 and 0.38 mg/kg, bolus 0.10 and 0.11 mg/kg, morphine concentration: 32 and 20.5 (ng/ml^{-1}). Outcomes from this study showed pain scores of 74% in cyanotic infants VS 84% in acyanotic infants.
- Gall et al., 2001. This was a RCT with in total 30 patients (11-20 years old) undergoing spinal fusion and aimed to investigate the efficacy of a single dose of 0, 2, or 5 µg ITM followed by a PCA. Outcomes of this study were: in 0, 2 and 5 µg ITM: first 24 hour of PCA morphine consumption 49,19 and 12 mg.
- Kiffer et al., 2001. This was a double-blind, randomised study with in total 21 children > 6 years undergoing major abdominal or orthopaedic surgery and aimed to investigate the use of e.d preservative-free morphine (30 µg/kg) in a single injection after anaesthesia versus control group. The outcomes from this study were: e.d vs control - the time between the end of the surgery and the first use of the PCA device was 5.4 h vs 3.4 h. Pain scores and morphine requirements smaller ($p<0.05$)
- Bozkurt, 2002. This study involved 44 children aged 5-15 years, undergoing major genitourinary or lower abdominal surgery and aimed to investigate the quality of analgesia and stress suppression by e.d or i.v. morphine. Treatment consisted of one group receiving a total of 0.1 mg/kg per day morphine epidurally and group two a total of 0.56 ± 0.33 mg/kg per day morphine, i.v. Outcome of this study was: Pain relief with both techniques was adequate.
- Bozkurt et al., 2004. This study involved 32 children undergoing major thoracotomy for non-cardiac thoracic surgery and aimed to compare thoracic epidural morphine (TEP) vs postinduction (INF). Facial action coding system (FACES) pain scores assessed by nurses from five face drawings: 0 = no hurt; 5 = hurt worst. Treatment consisted of a single dose of 0.1 mg/kg in 0.2 ml/kg saline (TEP group) or morphine infusion at 0.002 mg/kg/h following bolus dose of 0.05 mg/kg postinduction (INF group). Outcomes from this study were: groups mean FACES pain Scores during first hour 1.7 vs 2.4 and after 24 hours 3 vs 1.8.
- Suominen et al., 2004. This study involved 71 patients after heart surgery with a

sternotomy incision and aimed to compare postoperative pain control between ITM treated patients and control. The treatment consisted of 20 µg/kg ITM at induction of anaesthesia or control (i.v. rescue morphine boli and infusion 20-60 µg/kg). The outcomes of this study were i.v. morphine dose versus in the ITM group: mean time for the first dose was 12.3 vs. 8.7 hours (p = 0.0003). No additional morphine was given in 3/36 vs 7/35 patients.

- Castillo-Zamora et al., 2005. This was a randomised study with a total of 45 children undergoing surgery because of hip dysplasia and aimed to investigate the duration of postoperative analgesia. Treatment consisted of e.d morphine 11.2, 15 or 20 µg/kg. Outcomes of this study were: mean duration of postoperative analgesia was 12, 13.1 and 14.2 in e.d morphine 11.2, 15 or 20 µg/kg.

However, this selection of literary references was not considered to be up-to-date with literature currently available. Therefore, the MAH submitted additional references to support this application:

The majority of preterm neonates are capable of glucuronidating morphine, but birth weight; gestational and postnatal age influence the glucuronidation capability. Term neonates, infants, and children are able to produce morphine glucuronides. For the reported pharmacokinetics parameters, a meta-analysis was made; volume of distribution, estimated to be 2.8 ± 2.6 l.kg, seems to be regardless of age, while half-life and clearance were found to be related to age. Half-life was estimated to be 9.0 ± 3.4 h in pre-term neonates, 6.5 ± 2.8 h in term neonates aged 0-57 days, and 2.0 ± 1.8 h for infants and children aged 11 days to 15 years. Clearance was estimated to be 2.2 ± 0.7 ml/min/kg for preterm neonates, 8.1 ± 3.2 ml/min/kg in term neonates aged 0-57 days, and 23.6 ± 8.5 ml/min/kg in infants and children more than 11 days old [Kart T, 1997]. Comment: It appears that pre-term neonates have to be regarded as a separate group with regard to half-life and clearance. Later, a population pharmacokinetic model was developed with the nonlinear mixed-effects modelling software NONMEM V, on the basis of 2159 concentrations of morphine and its glucuronides from 248 infants receiving intravenous morphine ranging in bodyweight from 500 g to 18 kg (median 2.8 kg). Formation clearances of morphine to its glucuronides and elimination clearances of the glucuronides were found to be primarily influenced by bodyweight, which was parameterised using an allometric equation with an estimated exponential scaling factor of 1.44. Additionally, a postnatal age of less than ten days was identified as a covariate for formation clearance to the glucuronides, independent of birthweight or postmenstrual age. Distribution volumes scaled linearly with bodyweight [Knibbe, 2009].

Another study investigated clinical variables such as gestational age, sex, weight, the therapeutic regimens used and mechanical ventilation that might affect morphine requirements and plasma concentrations of morphine and its metabolites. In this double-blind study, neonates and infants stratified for age [group I 0-4 weeks (neonates), group II > or =4-26 weeks, group III > or = 26-52 weeks, group IV > or =1-3 years] admitted to the paediatric intensive care unit after abdominal or thoracic surgery received morphine 100 µg/kg after surgery, and were randomly assigned to either continuous morphine 10 µg/kg/h or intermittent morphine boluses 30 µg/kg every three hours. Pain was measured using the

COMFORT behavioural scale and a visual analogue scale. Additional morphine was administered on guidance of the pain scores. Morphine, M3G and M6G plasma concentrations were measured before, directly after, and at six, 12 and 24 hours after surgery. Multiple regression analysis of different variables revealed that age was the most important factor affecting morphine requirements and plasma morphine concentrations. Significantly fewer neonates required additional morphine doses compared with all other age groups ($p<0.001$). Method of morphine administration (intermittent vs continuous) had no significant influence on morphine requirements. Neonates had significantly higher plasma concentrations of morphine, M3G and M6G (all $p<0.001$), and significantly lower M6G/morphine ratio ($p<0.03$) than the older children. The M6G/M3G ratio was similar in all age groups [Bouwmeester NJ, 2003a].

A randomised double-blind study in the paediatric surgical intensive care unit was carried out by the same group to investigate age-related differences in morphine requirements and metabolism in 68 full-term neonates (52 aged under seven days, 16 aged seven day or older) following major surgery. After surgery patients were randomly assigned to continuous morphine (10 µg/kg per hour) or intermittent morphine (30 µg/kg per three hours). Additional morphine was administered on guidance of pain scores. Pain was measured by the Comfort behavioural scale and visual analogue scale. Morphine and M6G plasma concentrations were determined before and 0, six, 12, and 24 hours after surgery. The younger neonates differed significantly from the older neonates in morphine requirement (median 10 vs. 10.8 µg/kg per hour), morphine plasma concentration [23.0 vs. 15.3 ng/ml), and M6G/morphine ratio (0.6 vs. 1.5). Pain scores did not differ between age groups or morphine treatment groups. Neonates who were mechanically ventilated longer than 24 hours had significantly higher morphine plasma concentrations than the spontaneously breathing neonates 12 and 24 hours after surgery (29.1 vs. 13.1 ng/ml and 26.9 vs. 12.0 ng/ml, respectively). Morphine plasma concentrations were not correlated with analgesia or respiratory depression. Five neonates (intermittent morphine) showed respiratory insufficiency; however, the difference between the groups was not significant [Bouwmeester NJ, 2003a].

In a further investigation, postoperative children 0-3 years old were given an intravenous loading dose of morphine hydrochloride (100 µg/kg in two min) followed by either an intravenous morphine infusion of 10 µg/kg/h (n = 92) or three-hourly intravenous morphine boluses of 30 µg/kg (n = 92). Additional morphine (5 µg/kg every 10 min) was given if the visual analogue (VAS, 0-10) pain score was ≥ 4. Arterial blood (1.4 ml) was sampled within five minutes of the loading dose and at six, 12 and 24 hours for morphine, M3G and M6G. The disposition of morphine and formation clearances of morphine base to its glucuronide metabolites and their elimination clearances were estimated using non-linear mixed effects models. The analysis used 1856 concentration observations from 184 subjects. Population parameter estimates and their variability (%) for a one-compartment, first-order elimination model were as follows: volume of distribution 136 (59.3) litres, formation clearance to M3G 64.3 (58.8) litres/hour, formation clearance to M6G 3.63 (82.2) litres/hour, morphine clearance by other routes 3.12 litres/hour per 70 kg, elimination clearance of M3G 17.4 (43.0) litres/h, elimination clearance of M6G 5.8 (73.8) litres/hour. All parameters are standardised to a 70 kg person using allometric 3/4 power models and reflect fully mature adult values. The volume of distribution increased exponentially with a maturation half-life of 26 days from 83 litres per 70 kg at birth; formation clearance to M3G and M6G increased with a maturation

half-life of 88.3 days from 10.8 and 0.61 litres/hour per 70 kg respectively at birth. Metabolite formation decreased with increased serum bilirubin concentration. Metabolite clearance increased with age (maturation half-life 129 days), and appeared to be similar to that described for glomerular filtration rate maturation in infants [Bouwmeester NJ, 2004].

Finally, fatty acid amide hydrolase (FAAH) degrades anandamide, an endogenous cannabinoid. It was hypothesised that FAAH variants would predict risk of morphine-related adverse outcomes due to opioid-endocannabinoid interactions. In 101 postsurgical adolescents receiving morphine analgesia, the authors prospectively studied ventilatory response to 5% CO2 (HCVR), respiratory depression (RD) and vomiting. Blood was collected for genotyping and morphine pharmacokinetics. The authors found significant FAAH-morphine interaction for missense (rs324420) and several regulatory variants, with HCVR ($p < 0.0001$) and vomiting ($p = 0.0339$). HCVR was more depressed in patients who developed RD compared with those who did not ($p = 0.0034$), thus FAAH-HCVR association predicts risk of impending RD from morphine use [Chidambaran V, 2017].

In conclusion, the morphine-3-glucuronide metabolite has lower clearance, a shorter half-life and a smaller distribution volume compared with the morphine-6 metabolite, which is the most active morphine-like agonist. Neonatal pain relief may require a blood level of approximately 120 ng/ml, whereas lower levels (20-40 ng/ml) seem adequate for children. Morphine is extensively glucuronidated and sulphated at positions three and six, and that the glucuronidation rate is lower in younger neonates compared with older infants [Pacifici GM, 2016].

BACKGROUND: Standardizing concentrations of intravenous infusions enables pre-preparation and is effective in improving patient safety by avoiding large deviations from the prescribed concentration that can occur when infusions are made individually in wards and theatres. The use of pre-prepared morphine standardised concentration infusions for paediatric nurse/patient-controlled analgesia (N/PCA) has been investigated, with the to establish, implement and evaluate standardised concentrations of morphine in pre-filled syringes (PFS) for use in paediatric N/PCA. During the implementation, 175 morphine pre-prepared infusions were administered to 157 children (9.4 ± 5.1 years) in theatres and wards. Time taken to set up a N/PCA was 3.7 ± 1.7 min, a reduction of one third compared with the previous system. The number of incidents associated with N/PCA infusions was reduced by 41.2%, and preparation errors were eliminated. HCPs reported using morphine PFS was an easier and safer system [Rashed AN, 2019].

<u>Systematic reviews</u>

A systematic review aimed to evaluate the available literature examining different paediatric morphine regimens with respect to dosage, analgesic efficacy and incidence of side effects. 36 randomised, double-blind controlled clinical trials with 49 comparisons, including multiple dosage regimens and routes of administration were included. The primary outcome measures for analgesic efficacy (pain intensity, time to first analgesic request and need for rescue analgesics) together with the incidence of morphine-related side effects were evaluated qualitatively by significant difference ($p < 0.05$) as reported in the original investigations. Overall, significant improvements in the defined outcome measures on analgesic efficacy were only observed when morphine was compared with inactive control interventions. No

relation between morphine dosage and analgesic efficacy was detected. The most common morphine-related side effects were vomiting and sedation, with significantly higher incidences observed after morphine administration in half of all comparisons [Duedahl TH, 2007].

The aim of a study was to conduct an overview of systematic reviews that summarises the results about efficacy and safety from randomised controlled trials involving the various strategies used for postoperative pain management in children. The authors searched the Cochrane Database of Systematic Reviews, CINAHL, Database of Reviews of Effect, Embase, MEDLINE, and PsycINFO from the earliest date to January 24, 2016. This overview included 45 systematic reviews that evaluated interventions for postoperative pain in children. Out of 45 systematic reviews that investigated various interventions for postoperative pain in children, 19 systematic reviews (42%) presented conclusive evidence of efficacy. Positive conclusive evidence was reported in 18 systematic reviews (40%) for the efficacy of diclofenac, ketamine, caudal analgesia, dexmedetomidine, music therapy, corticosteroid, epidural analgesia, paracetamol, and/or nonsteroidal anti-inflammatory drugs and transversus abdominis plane block. Only one systematic review reported conclusive evidence of equal efficacy that involved a comparison of dexmedetomidine vs morphine and fentanyl. Safety of interventions was reported as conclusive in 14 systematic reviews (31%), with positive conclusive evidence for dexmedetomidine, corticosteroid, epidural analgesia, transversus abdominis plane block, and clonidine. Seven systematic reviews reported equal conclusive safety for epidural infusion, diclofenac intravenous vs ketamine added to opioid analgesia, bupivacaine, ketamine, paracetamol, and dexmedetomidine vs intravenous infusions of various opioid analgesics, oral suspension and suppository of diclofenac, only opioid, normal saline, no treatment, placebo, and midazolam. Negative conclusive statement for safety was reported in one systematic review for caudal analgesia vs non-caudal regional analgesia. More than half of systematic reviews included in this overview were rated as having medium methodological quality. Of 45 included systematic reviews, ten were Cochrane reviews and they had higher methodological quality than non-Cochrane reviews [Boric K, 2017].

Clinical trials

An observational study described the titration of morphine postoperatively in children in terms of the bolus dose, the number of boluses required, the time to establish analgesia, and side effects noted. Morphine was administered if pain score (VAS or FLACC1) was >30 in 103 children aged 0.8 -12.2 years (median age was 4.2 years). Patients weighing less than 45 kg received a 50 µg/kg bolus of morphine with subsequent boluses of 25 µg/kg as required. Patients weighing over 45 kg received boluses of 2 mg. Pain and Ramsay scores were recorded up to 90 minute after the end of the titration and any side effect or complication was noted. Data were presented as the median [interquartile Q1-Q3 range]. The median weight was 15.5 kg [8.2-35.0 kg]. The protocol was effective for pain control with a significant decrease in pain scores over time. The median pain score (VAS or FLACC) was 70 [50-80] prior to the initial bolus and 0 [0-10] 90 minutes after the last bolus. Median Ramsay score was 1 [1-2] before the initial bolus administration and 4 [2-4] at 90 minutes. The median total dose of morphine was 100 [70-140] µg/kg, and the median number of boluses was 3 [2-5]. Side effects were observed in 17% of cases (table 6). No serious complications were observed [Bernard R, 2014].

Table 7. Side effects occurring during morphine titration. Among 103 patients, 34 protocol violations were noted.

	n (%)
Patients with at least one side effect	17 (17)
Nausea and vomiting	9 (9)
Oxygen desaturation	6 (6)
Bradypnea	2 (2)
Urinary retention	(2)
Itching and allergy	0
Protocol compliance and occurrence of complications	8/69 (12)
Protocol violation and occurrence complications	9/34 (26.5)

In another observational study, the medical records of consecutive preterm neonates undergoing laser treatment of ROP from June 2007 through September 2010 were retrospectively reviewed. Because a fentanyl-based infusion protocol was initiated in November 2009, there was approximately the same number of treatment sessions with morphine and with fentanyl. In both groups, midazolam was used additionally on a case-by-case basis. Analgesia type, complications, and vital signs were documented at 5-minute intervals for all surgeries. The primary outcome was change in ventilation status. Secondary complications included change in temperature and incidence of apnoeic, bradycardic, and desaturation events. A total of 35 patients were included, with 17 in the morphine group (mean gestational age, 24.8 weeks; mean birth weight, 661 g) and 18 in the fentanyl group (mean gestational age, 24.4 weeks; mean birth weight, 681 g). Overall worsening of ventilation status was noted in 29% of patients in the morphine group and 6% of patients in the fentanyl group (P = 0.08; 95% confidence interval, -2% to 48%). Temperature instability (outside of 36.5° to 37.4°C range) was noted in 6% of patients in the morphine group and no patients in the fentanyl group. Apnoeic events were 3.2 times more common and bradycardic events 1.5 times more common in the morphine group [Orge FH, 2013].

To test the efficacy and safety of caudal anaesthesia (CA) supplemented by low dose morphine in children who undergo renal surgery, forty patients aged two months-14 years were enrolled and randomly divided into two groups of 20 patients each: group A (bupivacaine 0.2% with fentanyl); group B (bupivacaine with morphine). The duration of surgery and hospitalization time were recorded. Postoperative pain score was measured by FLACC scale and Wong-Baker Faces scale for those who are older. Overall use of rescue analgesics was calculated. There was no statistical difference in the length of surgery, incidence of pruritus, postoperative nausea, vomiting and urinary retention between the two groups. However, the postoperative opioid requirements were significantly higher in group A 1.03 ± 0.9 mg/kg compared to group B, in which only one patient required opioid therapy ($p < 0.0001$). Moreover, the need for non-opioid rescue analgesic was higher in group A, (36 ± 5.7 mg/kg of paracetamol) compared to

morphine CA group there only 26 ± 3.6 mg/kg required during first 24 h of the postoperative period (p = 0.0312). The FLACC pain score (1, 4, and 24 h after surgery) and Wong-Baker Faces scale were significantly higher in group A. The hospitalization period was shorter in the CA morphine group, but the difference did not reach statistical significance. None developed hemodynamic instability or respiratory depression [Chertin B, 2016].

Another study compared the delivery of morphine either via intravenous route (morphine i.v.) or via PCA device (morphine PCA) on risk of cardiopulmonary resuscitation (CPR) and mechanical ventilation (MV) using a large administrative database in the paediatric population. The authors assembled a retrospective cohort of paediatric inpatients between five and 21 years old in 42 children's hospitals between 2007 and 2011 from the US Paediatric Health Information System database. After propensity score matching, they created matched cohorts of morphine PCA and morphine IV patients, in both surgical and nonsurgical samples, who were similar on demographic, clinical, and hospital-level factors. They examined if PCA administration was associated with greater likelihood of CPR or MV up to two days after drug administration. Surgical and nonsurgical patients administered morphine PCA generally had lower odds of having MV on the baseline day and up to two days after PCA exposure, although these estimates were not statistically significant. Similarly, PCA exposure was associated with about 20%-44% lower odds of same day CPR in both surgical and nonsurgical patients, with a slightly greater reduction in the odds of CPR in the surgical patients [Faerber J, 2017].

Finally, to examine the safety and efficacy of nurse-controlled analgesia (NCA) in neonates less than one year of age, data from patients (one year of age receiving NCA as ordered by the Acute Pain Service at the Ohio State University College of Medicine) were collected over a five-year period and reviewed retrospectively. The primary outcomes were activation of the institution's Rapid Response Team (RRT) or Code Blue, signifying severe adverse events. Pain score after NCA initiation was a secondary outcome. Among 338 girls and 431 boys, the most common opioid used for NCA was fentanyl, followed by morphine and hydromorphone. There were 39 (5%) cases involving RRT or Code Blue activation, of which only one (Code Blue) was activated due to a complication of NCA (apnoea). Multivariable logistic regression demonstrated morphine NCA to be associated with greater odds of RRT activation (OR=3.29, 95% CI = 1.35, 8.03, p = 0.009) compared to fentanyl NCA. There were no statistically significant differences in pain scores after NCA initiation across NCA agents [Walia H, 2016].

Overall, the data indicates that in neonates and children a lower dose is recommended, and that preterm neonates should be considered as a separate group, for which the dose should be more pronounced lowered. The efficacy of morphine in children younger than one year has been demonstrated based on provided studies and systematic reviews.

IV.4 Clinical safety

Pain management with opioids requires adequate analgesia without severe adverse events. By these criteria, a substantial minority of treated patients do not have a successful outcome because of either severe side effects or inadequate analgesia, or a combination of both. The most common opioid-induced adverse events are summarised in the table below.(Cherny et al., 2001)

Table 8. Common opioid-induced side effects

Gastrointestinal	Nausea
	Vomiting
	Constipation
Autonomic	Xerostomia
	Urinary retention
	Postural hypotension
CNS	Drowsiness
	Cognitive impairment
	Hallucinations
	Delirium
	Respiratory depression
	Myoclonus
	Seizure disorder
	Hyperalgesia
Cutaneous	Itch
	Sweating

IV.4.1 Adverse events

To assess the effect of the type of opioids on the incidence of side effects from short-term opioids use, a retrospective study on 8855 subjects aged 16 years and older was conducted. Measurements were made to evaluate the presence of nausea and vomiting and respiratory depression. The patients received meperidine, morphine or fentanyl. 26% of the subjects suffered from nausea and vomiting, 1.5% showed respiratory depression after administration of opioids. Meperidene produced less nausea, vomiting and less respiratory depression than morphine. The risk of respiratory depression increased with age; patients aged 61 to 70 had 2.8 times higher risk than patients aged 16 to 45 years. Patients aged between 71 and 80 had 5.4 times the risk and those aged older than 80 years had 8.7 times the risk. (Cepeda et al., 2003)

Respiratory system

Respiratory depression is the most serious side effect, and death from an opiate overdose almost always occurs due to respiratory arrest. Opiates depress all phases of respiratory activity: rate, volume, and tidal change. Respiratory depression is of central origin, as the μ2-receptors in the brainstem respiratory centre mediate the effect. At the beginning of morphine therapy, also therapeutic doses may induce a dose dependent respiratory depression, which may lead to apnoea. In patients habituated to morphine, only a large

increase in dose may lead to respiratory depression, and apnoea is extremely rare. Depending upon the severity of respiratory depression, opiate dose reduction or antagonist administration are effective remedies. Patients suffering from renal insufficiency - which may cause an accumulation of morphine metabolites - may develop severe states of respiratory depression under morphine therapy. (Sjögren & Eriksen, 1994)

Osborne et al., 1986 described three patients with prolonged respiratory depression after treatment with morphine (40 to 198 hours after discontinuation of morphine) in the presence of impaired renal function, although no more morphine (and morphine-6-glucuronide) was detectable in the plasma.

To study the influence of morphine on the chemical control of breathing relative to the analgesic properties of morphine, a study was performed in 16 patients receiving either 0.2mg/kg morphine or placebo in a 90 second. infusion. At regular time intervals, respiratory variables (breathing, and the isocapnic acute hypoxic response), pain tolerance, and arterial blood samples were obtained for 24 hours. Placebo had no systematic effect on analgesic or respiratory variables. The results indicated that morphine tends to produce respiratory depression already at concentrations not causing any analgesic effect. At higher morphine concentrations (10-100 nM), the gain in analgesic effect is greater than the gain in respiratory depression. The authors conclude that despite lack of good pain relief, moderate to severe respiratory depression remains possible during morphine treatment. (Dahan et al., 2004)

Nervous system

Sedation is a dose-dependent effect of opiates. It is frequent at the beginning of the therapy and when doses are increased. Sedation is a central phenomenon, which is not synonymous to impaired psychomotor and cognitive function. Sleep disturbances, hallucinations and mental clouding are rather common side effects to which elderly patients are at particular risk. The conditions can be characterised from mild confusional states to acute psychotic conditions with visual hallucinations and nightmares. The site of action of these psychotomimetic effects is thought to be opiate receptors in cortical neurons and receptors in hypothalamic and temporal regions. Mood is significantly affected during opiate therapy. In particular, psychological tests on drug addicts or former drug addicts showed decreasing euphoria and sedation and loss of motivation for physical, mental, social, and sexual activities after chronic administration.(Sjögren & Eriksen, 1994)

In 1987, D'Souza reported a rare side effect of the morphine therapy which was observed in a 68 year-old patient who was treated with 30 mg morphine in prolonged release formulation because of a carcinoma of the prostate and metastases in the spinal column. Within 24 hours, a psychotic condition with delusions and anxiety developed, until the patient was finally stuporous. The patient had been hospitalised with suspected meningitis carcinomatosa. After discontinuation of morphine, his condition improved following administration of an antidepressant drug in combination with 40 mg of flupentixol. When morphine-retard was administered six weeks later because of an increase of pain, a psychotic condition developed again within few hours. The intake of morphine may further lead to conditions of anxiety, delirium, disorientation, reduced reactivity, euphoria (and dysphoria), hallucinations, increase in intracranial pressure, lack of concentration, headache, convulsions, lethargy, loss of libido, debility, and tremor. (Arzneimittelkursbuch, 2002/2003)

Some clinical reports suggest a relationship between the occurrence of hyperalgesia, allodynia and myoclonus and high-dose morphine treatment. Although only few clinical descriptions are available, experimental trials supports the notion that high morphine dosage may play a pathogenic role in the observed behavioural syndrome.

Six patients with malignant or non-malignant pain conditions were treated with moderate to high doses of oral, i.v. infusion or intrathecal morphine and developed hyperalgesia, allodynia and/or myoclonus. Blood or CSF samples were taken and analysed for contents of morphine and glucuronides. Comparing of the plasma and CSF concentrations from these patients to data from available literature of patients with none of these effects revealed a deviation of the values in five patients. In all six patients, the adverse events disappeared after substitution of morphine with another opioids or lowering the daily morphine dosage. (Sjögren & Eriksen, 1994; Sjogren et al., 1998)

Cardiovascular system

Morphine produces peripheral arterial and venous dilatation and tends to inhibit baroreceptor reflexes. Morphine-like opiates therefore should be used with caution in patients with decreased blood volume. Histamine liberation caused by morphine may also contribute to a decrease in blood pressure. In patients with coronary artery disease but no acute medical problems, 8 to 15 mg of morphine administered intravenously produces a decrease in O2- consumption, left ventricular end diastolic pressure, and cardiac work; effects on cardiac index are usually slight. Morphine effects on the myocardium are not significant in normal humans. In patients with acute myocardial infarction, the cardiovascular responses to morphine are generally similar; they may, however, be more variable than in normal subjects, and the magnitude of changes (e.g. the decrease in blood pressure) may be more pronounced. (Goodman and Gilman's 10th Ed., 2001)

Gastrointestinal system

The symptom of dry mouth is almost neglected in the literature, but this side effect constitutes a substantial clinical problem during long-term therapy. The clinical impression is that no tolerance develops. Constipation is the most common opiate side effect. The site of action is mainly peripheral at receptor sites in the gut and spinal cord thus decreasing intestinal secretions and peristaltics. There is no development of tolerance to opiate induced constipation. Laxatives have to be administered concomitantly (Sjögren & Eriksen, 1994) and prophylactically.

Nausea and vomiting occur in a large number of patients initially exposed to opiates, but tend to decrease or disappear with continuing opiate use. The aetiology may be found in a stimulation of the chemoreceptor trigger zone (in the area postrema of the medulla), in increased vestibular sensitivity and delayed gastric emptying. Constipation resulting from opioids, which is a frequent cause of nausea and vomiting in terminally ill patients, is dose-related and patients do not develop tolerance to this side effect. Prophylaxis is crucial because opioids-induced constipation is much easier to prevent than to treat. All patients should be prophylactically given a gastrointestinal motility stimulant laxative and stool softener, unless the use of these drugs is contraindicated. Stool softeners alone are not sufficient to alleviate opioid-induced constipation. (Ross and Alexander, 2001)

The data of 206 patients was retrospectively analysed to evaluate the frequency of constipation in palliative patients and patients receiving morphine. 159 subjects were treated with morphine. 42.7% of all patients suffered from constipation, 34% of those treated with morphine. No correlation between constipation and gastrointestinal tumours was observed. 74.3% of the patients received laxative drugs. Administration of macrogol in combination with treatment of patients with morphine-induced constipation. (Wirz and Klaschik, 2003)

Urinary system
Difficulty with micturition is mediated through central as well as peripheral opioid receptors situated in the spinal cord and in the bladder, respectively. There is evidence that tolerance to this effect develops, as the clinical problem is more evident during short-term use of opiates such as postoperative pain treatment. (Sjögren & Eriksen, 1994)

Skin
Pruritus of the skin is observed relatively often. It is associated with the capacity of μ-agonist opiates to release histamine. Normally, pruritus constitutes no clinical problem and may be treated with antihistaminergic drugs. (Sjögren & Eriksen, 1994)

Eyes
The miotic action of morphine on the eye was examined by Murray et al., 1983. 10 to 30 mg of morphine, administered i.m., caused miosis in all cases. As a method of examination, individual photographs of the pupils were used. The miotic effects could be reversed by applications of naloxone.

Cognition
A major concern in chronic use of morphine relates to possible cognitive side-effects. A long term prospective study in 28 subjects was conducted to assess the cognitive impact of oral sustained-release morphine in patients with non-cancer pain. Several neuropsychological tests were performed to explore attention, psychomotor speed and memory at baseline in patients free from opioids and then after three, six and 12 months. 18 patients received oral sustained-release morphine in doses of 40-140 mg/day, ten patients stopped morphine intake prematurely due to side effects or insufficient pain relief and were followed as control group. No impairment of any neuropsychological variable over time was observed compared to the control group. (Tassain et al., 2003)

IV.4.2 Serious adverse events

Overdosage
It is suggested that in the case of morphine, a normal, pain-free adult is not likely to die after oral doses less than 120 mg, or to have serious toxic symptoms with less than 30 mg parenterally (Goodman and Gilman's 10th Ed., 2001). Dose increases (> 30 % of daily dose) during long-term opiate therapy in patients with cancer could lead to cognitive impairment, which should be resolved within a few days (Sjögren & Eriksen, 1994).

In states of overdosage, drowsiness must be reckoned with; extreme overdosage will lead to a state of deep coma. The signs of an overdosage are respiratory depression (decrease of

respiratory rate, decrease of tidal volume and tidal change), cyanosis, decrease in blood pressure, pin-head pupils, reduced excretion of urine, and dropping of the body temperature. In case of epidural or intrathecal administration, respiratory depression and arrest may occur even with small doses of morphine. Special care has to be given in respiratory monitoring.

Respiratory depression is the most serious side effect, and death from an opiate overdose is almost always due to respiratory arrest. Therapeutic measures for the treatment of a morphine overdose are: O2-enriched air, artificial respiration, and/or administration of the morphine antagonist naloxone, whereby doses 0.4 mg of naloxone are slowly injected intravenously. As naloxone has a shorter duration of action than morphine, repeated doses over a longer period of time may be necessary. For children, the initial dose of naloxone is 0.01 mg/kg parenterally (Goodman and Gilman's 10th Ed., 2001).

In 1985, Blain et al. report about a young man who had taken 1800 mg of MST Continus (morphine in a slow release formulation) and an unknown amount of metoclopramide. When he was hospitalised, he was in a state of drowsiness, but followed orders; further, a marked miosis and tendon hyporeflexia were observed. His respiratory rate was at about six per minute and the respiratory minute volume about six litres. Apart from a mild hypoxia and a slight acidosis, the serum creatinine value was elevated (131 µmol/l). The plasma-myoglobin concentration, which was determined five hours after the hospitalization, was about 550µg/l (normal value < 60 µg/l). A determination of the plasma morphine concentration 12 hours after the hospitalization showed a morphine level of 60 µg/l. By means of further follow-up examinations, it could be determined that the agent has a plasma half-life of more than nine hours. With the laboratory results this patient was considered to have morphine overdosage induced rhabdomyolysis. The patient survived with i.v. naloxone, improving his conscious level and normalizing respiration.

Acquired tolerance and dependence

Tolerance is a pharmacological effect and is characterised by the need for increased doses in order to maintain the analgesic effect. Tolerance and physical dependence after repeated opioid administration are characteristic features of all opioid agonists and are among the major limitations to their clinical use. Cross-tolerance develops between all the opioids. Tolerance can occur without physical dependence, but the reverse does not seem to occur. (Stoelting, 1990) It is important to remember that, from the patients' point of view, tolerance will be registered as a gradual increase in pain. Tolerance to morphine may primarily involve only the µ-receptors. (Sjögren & Eriksen, 1994) Often the need for increased doses reflects advancement of disease or increased psychological distress rather than tolerance to the analgesic effect. (Warfield, 1993)

Physical dependence on opiates is defined by the appearance of withdrawal symptoms when the opiate is too quickly discontinued, or when an opiate antagonist is administered. Clinically pain patients will often not be aware of having withdrawal symptoms, and will describe these symptoms as increased pain. The withdrawal symptoms seen after µ-opioid agonists are qualitatively similar, but may differ in time and onset, and in duration and intensity. Clinical signs and symptoms of withdrawal are sneezing, flow of tears, tachypnoea, yawning, crises of blood pressure, circulatory failure, profuse sweating, "chicken-skin", diarrhoea, vesical spasms, pains in the abdomen and the extremities, hyperactivity, and irritability characterised

by symptoms of central excitement (aggression, dysphoria and insomnia). This withdrawal syndrome can also be caused by the morphine antagonist naloxone. (Jurna, 1992) Time course is related to the half-life of the drug and its receptor affinity. It is recommended that patients should be given a gradually reduced dose of the opiates, using a 10% reduction every day until no drug is needed. (Sjögren & Eriksen, 1994; Foley, 1993) Psychological dependence may be present independent of both tolerance development and physical dependence. It is not simply related to chronic use alone, but to a series of individual and social factors (Foley, 1993).

Development of dependence

Morphine tolerance is an adaptation process resulting from a desensitisation of opioids receptors. In addition, a number of non-opioid mechanisms contributing to the development of tolerance have been established, involving glial cells, Nmethyl-D-aspartate, cyclic aminomonophosphate, α-calcitonin gene-related peptide, orphanin FQ/nociceptin, serotonin, cholcystokinin, and several others. The presence of an ongoing painful condition does not prevent the rapid and profound development of opioids tolerance. While it is generally accepted that tolerance to opioids analgesia does occur, it does not appear to be a limiting factor. Dose escalation in chronic pain therapy is considered to be predominantly a consequence of increasing pain as a result of nociceptive input as the disease progresses. (Streltzer J, 2001)

Pain management in opioid-dependents

Management of chronic pain patients dependent on opioids is the most difficult and controversial area of pain management. Chronic opioids intake may enhance pain sensitivity. Acute and terminal pain in the opioid-dependent patient is generally manageable, however, with higher opioids doses. For the opioids-dependent patient, opioids are typically ineffective. For patients it is difficult to resist the immediate relative increase in comfort. Long-term treatment is associated with substantial risks, including accident proneness, unnecessary invasive procedures and tests, adverse health consequences, impaired judgement and cognitive function, decline in occupational and social functioning, and strained family relationships. If dependent patients do not seek outside sources of opioids, pain management that eliminates the opioids can result in satisfying improvements in pain and function. (Streltzer J, 2001; Freye and Latasch, 2003)

In order to avoid unnecessary further development of tolerance, simultaneous administration of other receptor mediated analgesics is advocated as soon as tolerance to the analgesic effect is observed. Preoperative strategies aim at multimodal analgesic concepts which consist of the simultaneous administration of low-dose ketamine, co-administration of an α2-agonist, and the administration of a selective COX-2-inhibitor, respectively. In chronic pain therapy, combined administration with either dextromethorphane, or opioids rotation of a more potent ligand is suggested. In intensive care, co-administration of an α2-agonist, and daily intermittent cessation of benzodiazepine administration are advocated. (Freye and Latasch, 2003)

Neonatal abstinence syndrome (NAS)

NAS is suffered by infants withdrawing from substances on which they have become physically dependent due to in utero exposure. They may require prolonged treatment and spend weeks or even months in hospital. A wide range of drugs have been used in the treatment of NAS.

There is evidence suggesting opioids to be most appropriate, at least in infants exposed to diamorphine or methadone. Diazepam has been shown to be ineffective. Morphine and methadone are currently the most commonly prescribed opioids to treat NAS. Further research is necessary to evaluate whether a single opiate or a multiple drug regimen is the best option for infants with NAS (Johnson et al., 2003).

NAS due to opiate withdrawal may result in the disruption of the mother-infant relationship, sleep-wake abnormalities, feeding difficulties, weight loss and seizures. Treatments used to ameliorate symptoms and reduce morbidity include opiates, sedatives and nonpharmacological treatments. The efficacy and safety of using morphine compared to a sedative or non-pharmacological treatment in the treatment of NAS due to withdrawal from opiates was evaluated. Morphine appears to reduce the time to regain birth weight and reduce the duration of supportive care, but to increase the duration of hospital stay; there is no evidence of effect on treatment failure. Compared to phenobarbital, morphine may decrease the incidence of seizures although there is no evidence of effect on treatment failure. Compared to diazepam, morphine reduces the incidence of treatment failure. The hypothesis is generated that treatment effects may vary according to whether population includes infants born to all opiate users or is restricted to infants of mothers who used morphine only. Further research is urgently necessary (Osborn et al., 2002).

Furthermore, the MAH carried out a further and more extensive literature search about adverse drug reactions of morphine on each organ class:

- Psychiatric disorders: In general, morphine induces sedation, feelings of dejection, anxiety, insecurity and slowed performance in healthy, pain-free, opioid-naïve volunteers, but little feeling of well-being and euphoria. It is assumed that the often-claimed induction of euphoria, the 'high', depends very much on the personality of the drug user and their drug history [Schug SA, 1992]. These effects tend to occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain. The euphoric activity of opioids has led to their abuse [Martindale, 2020].
- Immune system disorders: Morphine and some other opioids have a dose-related histamine-releasing effect which may be responsible in part for reactions such as urticaria and pruritus as well as hypotension and flushing. Anaphylactic reactions after intravenous injection have been reported rarely [Martindale, 2020].
- Metabolism and nutrition disorders: For opioids used to treat cancer pain adverse event incidence rates were 13% for anorexia [Wiffen PJ, 2014].
- Eye disorders: Miosis has been described as a possible adverse reaction of opioid analgesics. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops [Martindale, 2020]. A tendency towards a divergence of the visual axes appears to be present in opioid users, although when present it may not always lead to diplopia. Following detoxification intermittent esotropia or constant esotropia (convergence of the visual axes) can occur; if intermittent the angle tends to be small and diplopia present when viewing distance objects. Occlusion of one eye to eliminate the second image could encourage the development of a constant deviation. The deviation is not caused by a cranial nerve palsy. Constant deviations of this type are classified as 'acute acquired concomitant esotropia'. Relief from the diplopia may be gained by prismatic

correction, and the deviation may then resolve spontaneously [Firth AY, 2005]. Downbeat nystagmus has been reported as a manifestation of morphine toxicity. Epidural morphine has also been implicated in the appearance of vertical nystagmus [Korff C, 2007].

- Vascular disorders: A recent Cochrane review found significantly increased risk ratios with opioids compared to placebo for hot flushes [Els C, 2017]. Orthostatic hypotension has described as a possible adverse reaction of opioid analgesics [Martindale, 2020].
- Respiratory, thoracic and mediastinal disorders: Large doses of opioids produce respiratory depression. Death may occur from respiratory failure. Toxic doses of specific opioids vary considerably with the individual and regular users may tolerate large doses. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage. Pulmonary oedema after overdosage is a common cause of fatalities among opioid addicts [Martindale, 2020].
- Gastrointestinal disorders: In usual doses the commonest adverse effects of opioid analgesics, including morphine, are nausea, vomiting, and constipation [Martindale, 2020]. Opioid-induced bowel dysfunction (OIBD) is characterised by constipation, incomplete evacuation, bloating, and gastric reflux. It is one of the major adverse events of treatment for pain in cancer and in palliative care, resulting in increased morbidity and reduced quality of life. Estimated incidence of OIBD in hospice populations and people with advanced disease is high from 65% to 90% [Candy B, 2018].
- Hepatobiliary disorders: Morphine can cause an increase in intra-biliary pressure as a result of effects on the sphincter of Oddi and may therefore be expected to exacerbate rather than relieve pain in patients with biliary colic or other biliary-tract disorders [Martindale, 2020]. Biliary-type pain after cholecystectomy has also been associated with morphine [Roberts-Thompson IC, 1990].
- Skin and subcutaneous tissue disorders: Morphine and some other opioids have a dose-related histamine-releasing effect which may be responsible in part for reactions such as urticaria and pruritus. Contact dermatitis has been reported and pain and irritation may occur on injection [Martindale, 2020]. Paresthesias have been reported after epidural administration in a small percentage of patients (6.9%) [Heo BH, 2014].
- Renal and urinary disorders: Micturition may be difficult and there may be ureteric spasm after morphine [Martindale, 2020]. An antidiuretic effect of morphine has been described in animals [Tsushima H, 1987], but no mention of this action has been found in clinics.
- Reproductive system and breast disorders: In a study, decreased libido or impotency was present in 23 of 24 men receiving opioids. The serum testosterone level was below 9 nmol/L in 25 of 29 men and was significantly lower than that in the control group ($p < 0.001$). Decreased libido was present in 22 of 32 women receiving opioids. All 21 premenopausal females developed either amenorrhea or an irregular menstrual cycle, with ovulation in only one. About 15% developed central hypocorticism, and about 15% developed GH deficiency [Abs R, 2000].

Overall the common adverse events, serious adverse events, overdosing and dependence development are discussed adequately. Moreover, data on system organ classes of

cardiovascular system, immune system disorders, eye disorders, gastrointestinal disorders, hepatobiliary disorders and metabolism and nutrition disorders, are updated in the clinical overview, based on recent scientific literature. This is agreed.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Morfine HCL Focus.

Summary table of safety concerns as approved in RMP

Important identified risks	• Respiratory depression • Physical dependence and withdrawal
Important potential risks	• Drug abuse • Accidental overdose • Use in patients with impaired renal function
Missing information	• Use in pregnancy and breastfeeding

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

This national procedure concerns a well-established use application for Morfine HCl Focus. For this authorisation, reference is made to literature. No new clinical studies were conducted. Risk management is adequately addressed. Altogether it is considered that efficacy of morphine hydrochloride trihydrate in the treatment severe pain has been established as the majority of studies in subjects showed statistically significant and clinically relevant results. Finally, it is considered that the safety issues that are identified are adequately addressed in the SmPC.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Vendal retard / Morphine hydrochloride trihydrate 10/30/60/100/200 mg prolonged-release tablets AT/H0103+0106/001-005/MR. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Morfine HCl 100 mg/10 ml Focus, Morfine HCl 200 mg/10 ml Focus and Morfine HCl 10 mg/ml Focus, solution for injection/infusion have a proven chemical-pharmaceutical quality. Morfine HCl Focus has an adequate efficacy and safety profile and is considered widely established.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Morfine HCl Focus with the reference product, and have therefore granted a marketing authorisation. Morfine HCl 100 mg/10 ml Focus and Morfine HCl 200 mg/10 ml Focus were authorised in the Netherlands on 27 October 2020. Morfine HCl 10 mg/ml Focus was authorised in the Netherlands on 6 December 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

LITERATURE REFERENCES

Abs R, Verhelst J, Maeyaert J, Van Buyten JP, Opsomer F, Adriaensen H, Verlooy J, Van Havenbergh T, Smet M, Van Acker K. Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab. 2000 Jun;85(6):2215-22. doi: 10.1210/jcem.85.6.6615. PMID: 10852454.

Agmo A, Paredes RG, Contreras JL. Opioids and sexual behavior in the male rabbit: the role of central and peripheral opioid receptors. J Neur Transm [Gen Sect] 1994; 97:211-23.

AHFS Drug Information 2020. www.medicinescomplete.com

Ahmadnia H, Akhavan Rezayat A, Hoseyni M, Sharifi N, Khajedalooee M, Akhavan Rezayat A. Short-Period Influence of Chronic Morphine Exposure on Serum Levels of Sexual Hormones and Spermatogenesis in Rats. Nephrourol Mon. 2016 Jul 3;8(4):e38052. eCollection 2016 Jul.

Aiello-Malmberg P, Bartolini A, Bartolini R, Galli A. Effects of morphine, physostigmine and raphe nuclei stimulation on 5-hydroxytryptamine release from the cerebral cortex of the cat. Br J Pharmacol 1979; 65:547-55.

Anagnostakis Y, Krikos Y, Spyraki C. Pallidal substrate of morphine-induced locomotion. Eur Neuropsychopharmacol 1992; 2:65-72.
analgesia in children. Can J Anaesth. 2002 Jan;49(1):67-71.

Arzneimittelkursbuch. Opioid-Analgetika. A.V.I. Arzneimittel-Verlags GmbH Berlin; 2002/2003, p. 1686-1709.

Bae J, Kim HC, Hong DM. Intrathecal morphine for postoperative pain control following robot-assisted prostatectomy: a prospective randomised trial. J Anesth. 2017 Aug;31(4):565-571.

Barke KE, Hough LB. Characterization of basal and morphine-induced histamine release in the rat periaqueductal gray. J Neurochem. 1994 Jul;63(1):238-44.

Bianchi G, Ferretti P, Recchia M, Rocchetti M, et al. Morphine tissue levels and reduction of gastrointestinal transit in rats. Gastroenterology 1983; 85:852-8.
Blain PG, Lane RJM, Bateman DN, Rawlins MD. Opiate-induced rhabdomyolysis. Human Toxicol 1985; 4:71-4.

Boulanger A, Perreault S, Choiniere M, Prieto I, Lavoie C, Laflamme C. Intrathecal morphine after cardiac surgery. Ann Pharmacother. 2002 Sep;36(9):1337-43.

Bowrey S, Hamer J, Bowler I, Symonds C, Hall JE. A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. Anaesthesia. 2005 May;60(5):449-52

Bozkurt P, Kaya G, Yeker Y, Altintas F, Bakan M, Hacibekiroglu M, Bahar M. Effectiveness of morphine via thoracic epidural vs intravenous infusion on postthoracotomy pain and stress response in children. Paediatr Anaesth. 2004 Sep;14(9):748-54.

Bozkurt P. The analgesic efficacy and neuroendocrine response in paediatric patients treated with two analgesic techniques: using morphine-epidural and patient-controlled analgesia. Paediatr Anaesth. 2002 Mar;12(3):248-54.

Brailowsky S, Guerrero-Munoz F, Luján M, Shkurovich M. Morphine-theophylline interaction: antagonism or facilitation? Br J Pharmacol 1981;73:887-92.
Brain Res 1982; 253:253-61.

Brown NJ, Coupar IM, Rumsey RDE. The effect of acute and chronic administration of morphine and morphine withdrawal on intestinal transit time in the rat. J Pharm Pharmacol 1988; 40:844-8.

Bucher K, Benz-Lippold M, Bättig P. Peak-potentialities of inspiratory musculature as disclosed by tracheal occlusion. Agents and Actions 1973; 3(1):28-34.

Campos AE, Luán M, López E, et al. Circadian variation in the lethal effect of morphine in the mouse. Proc West Pharmacol Soc 1983; 26:101-3.

Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Cochrane Database Syst Rev. 2018 Jun 5;6(6):CD006332. doi: 10.1002/14651858.CD006332.pub3. PMID: 29869799; PMCID: PMC6513061.

Carpenter GW, Garza HH, Gebhardt BM, Carr DJ. Chronic morphine treatment suppresses CTL-mediated cytolysis, granulation, and Camp

Castillo-Zamora C, Castillo-Peralta LA, Nava-Ocampo AA. Dose minimization study of single-dose epidural morphine in patients undergoing hip surgery under regional anesthesia with bupivacaine. Paediatr Anaesth. 2005 Jan;15(1):29-36.

Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther. 2003 Aug;74(2):102-12.

Chan MY, Dai S. Morphine treatment and intravenous glucose tolerance tests in mice. Pharmacol Res1989; 21(4):353-8.

Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, Mercadante S, Pasternak G, Ventafridda V; Expert Working Group of the European Association of Palliative Care Network. Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol. 2001 May 1;19(9):2542-54.

Chrubasik S & Chrubasik J Opiatwirkung über die Opiatrezeptoren. Deutsche medizinische Wochenschrift, 120(3):67-69, 1995

Cicero TJ, Adams ML, Giordano A, Miller BT, et al. Influence of morphine exposure during adolescence on the sexual maturation of male rats and the development of their offspring. J Pharmacol Exp Ther 1991; 256(3):1086-93.

Combie JD, Nugent TE, Tobin T. Pharmacokinetics and protein binding of morphine in horses. Am J Vet Res 1983;44(5):870-4.

Corli O, Floriani I, Roberto A, Montanari M, Galli F, Greco MT, Caraceni A, Kaasa S, Dragani TA, Azzarello G, Luzzani M, Cavanna L, Bandieri E, Gamucci T, Lipari G, Di Gregorio R, Valenti D, Reale C, Pavesi L, Iorno V, Crispino C, Pacchioni M, Apolone G; CERP STUDY OF PAIN GROUP (List of collaborators); CERP STUDY OF PAIN GROUP. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter

randomised phase IV 'real life' trial on the variability of response to opioids. Ann Oncol. 2016 Jun;27(6):1107-15.

Correll DJ, Viscusi ER, Grunwald Z, Moore JH Jr. Epidural analgesia compared with intravenous morphine patient-controlled analgesia: postoperative outcome measures after mastectomy with immediate TRAM flap breast reconstruction. Reg Anesth Pain Med. 2001 Sep-Oct;26(5):444-9.

D'Souza M Unusual Reaction to Morphine. The Lancet, 98, 1987

Dahan A, Romberg R, Teppema L, Sarton E, Bijl H, Olofsen E. Simultaneous measurement and integrated analysis of analgesia and respiration after an intravenous morphine infusion. Anesthesiology. 2004 Nov;101(5):1201-9.
Dev Brain Res 1992; 67:19-26. In: Forth, Henschler, Rummel und Starke. Pharmakologie und Toxikologie. BI Wissenschaftsverlag Mannheim; 1992, p.200 – 215.

Devys JM, Mora A, Plaud B, Jayr C, Laplanche A, Raynard B, Lasser P, Debaene B. Intrathecal + PCA morphine improves analgesia during the first 24 hr after major abdominal surgery compared to PCA alone. Can J Anaesth. 2003 Apr;50(4):355-61.

Diana M, Pistis M, Muntoni A, Gessa G. Profound decrease of mesolimbic dopaminergic neuronal activity in morphine withdrawn rats. J Pharmacol Exp Ther 1995; 272(2):781-5.

Dib B. A study of intrathecal self-injection of morphine by rats, and the difficulties entailed. Pain 1985; 23:177-85.

Domino EF, Dahlstrom BE, Domino LE, Domino SE. Relation of plasma morphine concentrations to severity of abrupt withdrawal in morphine dependent monkeys. J Pharmacol Exp Ther 1987; 243(1):138-43.

Duale C, Frey C, Bolandard F, Barriere A, Schoeffler P. Epidural versus intrathecal morphine for postoperative analgesia after Caesarean section. Br J Anaesth. 2003 Nov;91(5):690-4.

El Sherif FA, Othman AH, Abd El-Rahman AM, Taha O. Effect of adding intrathecal morphine to a multimodal analgesic regimen for postoperative pain management after laparoscopic bariatric surgery: a prospective, double-blind, randomised controlled trial. Br J Pain. 2016 Nov;10(4):209-216.

Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R, Sharma S, Kolahdooz F, Straube S. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2017 Oct 30;10(10):CD012509. doi: 10.1002/14651858.CD012509.pub2. PMID: 29084357; PMCID: PMC6485910.

Elsner F, Radbruch L, Loick G, Gartner J, Sabatowski R. Intravenous versus subcutaneous morphine titration in patients with persisting exacerbation of cancer pain. J Palliat Med. 2005 Aug;8(4):743-50.

Firth, A.Y. (2005) Heroin and diplopia. Addiction, 100 (1). pp. 46-50. ISSN 0965-214 https://doi.org/10.1111/j.1360-0443.2005.00915.x

Foley KM The Treatment of Cancer Pain. The New England Journal of Medicine, 313(2):84-95, 1985

Frenk H, Liban A, Balamuth R, Urca G. Opiate and non-opiate aspects of morphine induced seizures.

Freye E, Latasch L. Development of opioid tolerance -- molecular mechanisms and clinical consequences] Anasthesiol Intensivmed Notfallmed Schmerzther. 2003 Jan;38(1):14-26.

Fromherz K. Pharmacological effects of 3-hydroxy-N-methylmorphinan. Arch Int Pharmacodyn 1951; 535(3-4): 387-98.

Fujinaga M, Mazze RI. Teratogenic and postnatal developmental studies of morphine in Sprague-Dawley rats. Teratology 1988; 38(5):401-10.

Fuller GN, Lin SN, Caprioli RM, Wiggins RC, Dafny N. Dose-related differential accumulation of morphine in specific regions of rat brain determined by mass fragmentography. Int J Neurosci 1988; 38:31-8.

Funada M, Suzuki T, Sugano Y, Tsubai M, Misawa M, et al. Role of ß-adrenoceptors in expression of morphine withdrawal signs. Life Sci 1994; 54(8):PL113-8.

Gabrielsson JL, Paalzow LK. A physiological pharmacokinetic model for morphine disposition in the pregnant rat. J Pharmacokinet Biopharm 1983; 11(2):147-63.

Gall O, Aubineau JV, Berniere J, Desjeux L, Murat I. Analgesic effect of low-dose intrathecal morphine after spinal fusion in children. Anesthesiology. 2001 Mar;94(3):447-52.

Genc E, Havemann U, Tzoneva-Tyutyulkova N, Kuschinsky K. Motility, rigidity and turnover of dopamine in the striatum after administration of morphine to rats: a re-evaluation of their mechanisms. Neuropharmacology 1983; 22(4):471-6.

Gold LH, Stinus L, Inturrisi CE, Koob GF. Prolonged tolerance, dependence and abstinence following subcutaneous morphine pellet implantation in rat. Eur J Pharmacol 1994; 253:45-51.

Goodman and Gilman's: The Pharmacological Basis of Therapeutics. Gutstein HB, Akil H. 10th edition; 2001.

Greene RF, Miser AW, Lester CM, Balis FM, Poplack DG. Cerebrospinal fluid and plasma pharmacokinetics of morphine infusions in pediatric cancer patients and rhesus monkeys. Pain 1987; 30:339-48.

Habib AS, Muir HA, White WD, Spahn TE, Olufolabi AJ, Breen TW. Intrathecal morphine for analgesia after postpartum bilateral tubal ligation. Anesth Analg. 2005 Jan;100(1):239-43.

Hanks GW, Hoskins PJ, Aherne GW, Turner P, Poulain P. Explanation for potency of repeated oral doses of morphine? Lancet 1987; 2:723-5.

Harpel HS, Gautieri RF. Morphine induced fetal malformations I. J Pharm Sci 1968; 57(9):1590-7.

Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliat Med. 2003 Apr;17(3):248-56.

Henney RP, Vasko JS, Brawley RK, Oldham HN, et al. The effects of morphine on the resistance and capacitance vessels of the peripheral circulation. Am Heart J 1966; 72:242-50.

Heo BH, Pyeon TH, Lee HG, Kim WM, Choi JI, Yoon MH. Epidural Infusion of Morphine and Levobupivacaine through a Subcutaneous Port for Cancer Pain Management. Korean J Pain. 2014 Apr;27(2):139-44. doi: 10.3344/kjp.2014.27.2.139. Epub 2014 Mar 28. PMID: 24748942; PMCID: PMC3990822.

Horton TL, Pollack GM. Enterohepatic recirculation and renal metabolism of morphine in the rat. J Pharm Sci 1991, 80(12):1147-52.

Huidobro F, Croxatto R, Huidobro-Toro JP. Effect of morphine on the clearance of endogenous creatinine and blood clinical chemicals in the rat. Arch Int Pharmacodyn 1979; 237:31-41.

Huidobro F, Diez C, Croxatto R, Huidobro-Toro JP. Morphine antidiuresis in the rat: biphasic effect of the opiate on the excretion of urine electrolytes. J Pharm Pharmacol 1981;33:815-6.
Iwamoto K, Klaassen CD. First-pass effect of morphine in rats. J Pharmacol Exp Ther 1977; 200(1):236-44.

Jackson H. The evaluation of analgesic potency of drugs using thermal stimulation in the rat. Br J Pharmacol 1952; 7:196-203.

James RW, Heywood R, Crook D. Effects of morphine sulphate on pituitary-testicular morphology of rats. Toxicol Lett 1980; 7:61-70.

Johnson K, Gerada C, Greenough A. Treatment of neonatal abstinence syndrome. Arch Dis Child Fetal Neonatal Ed. 2003 Jan;88(1):F2-5.

Jurna I Analgetika - Schmerzbekämpfung. in: Forth Henschler, Rummel und Starke: Pharmakologie und Toxikologie BI Wissenschaftsverlag Mannheim, 1992: p200 - 215.

Jurna I. Analgetika - Schmerzbekämpfung. Pharmacol Res1989; 21(4):353-8.

Katagiri Y, Itakura T, Naora K, Kanba Y, Iwamoto K. Enhanced bioavailability of morphine after rectal administration in rats. J Pharm Pharmacol 1988; 40(12):879-81.

Kiffer F, Joly A, Wodey E, Carre P, Ecoffey C. The effect of preoperative epidural morphine on postoperative analgesia in children. Anesth Analg. 2001 Sep;93(3):598-600.
Kimura ET, Dodge PW, Young PR, Johnson RP. Pharmacologic studies with ABBOTT-30360, an analgesic-tranquilizer, and ist analogues. Arch Int. Pharmacodyn 1971; 190:124-34.

Kishioka S, Nishida S, Fukunaga Y, Yamamoto H. Quantitative properties of plasma corticosterone elevation induced by naloxone-precipitated withdrawal in morphine-dependent rats. Jpn J Pharmacol 1994; 66:257-63.

Kissin I, Brown PT, Robinson CA, Bradley EL. Acute tolerance in morphine analgesia: continuous infusion and single injection in rats. Anesthesiology 1991; 74:166-71.

Kong SK, Onsiong SM, Chiu WK, Li MK. Use of intrathecal morphine for postoperative pain relief after elective laparoscopic colorectal surgery. Anaesthesia. 2002 Dec;57(12):1168-73.

Kontani H, Kawabata Y. A study of morphine-induced urinary retention in anesthetised rats capable of micturition. Jpn J Pharmacol 1988; 48:31-6.

Korff C, Peter M, Burkhard PR. Downbeat nystagmus as a manifestation of intrathecal morphine toxicity. Eur J Anaesthesiol. 2007 Feb;24(2):201-2. doi: 10.1017/S0265021506001724. Epub 2006 Oct 11. PMID: 17038213.

LeVier DG, McCay JA, Stern ML, Harris LS, Page D, et al. Immunotoxicological profile of morphine sulphate in B6C3F1 female mice. Fundam Appl Toxicol1994; 22:525-42.

Lintern-Moore S, Supasri Y, Pavasuthipaisit K, Sobhon P. Acute and chronic morphine sulphate treatment alters ovarian development in prepuberal rats. Biol Reprod 1979; 21:379-83.

Lynn AM, McRorie TI, Slattery JT, Calkins D, Opheim KE. Pharmacokinetics and pharmacodynamics of morphine in infant monkeys. Dev Pharmacol Ther 1991; 16:41-7.

Lynn AM, Nespeca MK, Bratton SL, Shen DD. Ventilatory effects of morphine infusions in cyanotic versus acyanotic infants after thoracotomy. Paediatr Anaesth. 2003 Jan;13(1):12-7.

Manning BH, Morgan MJ, Franklin KB. Morphine analgesia in the formalin test: evidence for forebrain and midbrain sites of action. Neuroscience 1994; 63(1):289-94.

Martindale: The complete drug reference © 2017 Pharmaceutical Press. Morphine (monograph last updated: Dec-2016; accessed: Dec 2017]. http://www.medicinescomplete.com

Melzacka M, Neßelhut T, Havemann U, Vetulani J, Kuschinsky K. Pharmacokinetics of morphine in striatum and nucleus accumbens: relationship to pharmacological actions. Pharmacol Biochem Behav 1985; 23:295-301.

McNeill MJ, Ho ET, Kenny GN. Effect of i.v. metoclopramide on gastric emptying after opioid premedication. Br J Anaesth. 1990 Apr;64(4):450-2. doi: 10.1093/bja/64.4.450. PMID: 2334619.

Molina PE, Hashiguchi Y, Ajmal M, Mazza M, Abumrad NN. Differential hemodynamic, metabolic and hormonal effects of morphine and morphine-6- glucuronide. Brain Res 1994; 664:126-32.

Product monograph Kadian. 2018.

Murray RB, Adler MW, Korczyn AD The Pupillary Effect of Opioids. Life Sciences, 33(6):495-509, 1983

Murthy BR, Pollack GM, Brouwer KL. Contribution of morphine-6-glucuronide to antinociception following intravenous administration of morphine to healthy volunteers. J Clin Pharmacol. 2002 May;42(5):569-76.
Nature 1974; 247:376-7.

Oldendorf WH, Hyman S, Braun L, Oldendorf SZ. Blood-brain barrier: penetration of morphine, codeine, heroin, and methadone after carotid injection. Science 1972; 178:984-6.

Osborn DA, Cole MJ, Jeffery HE. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database Syst Rev. 2002;(3):CD002059.

Osborne RJ, Joel SP, Slevin ML Morphine intoxication in renal failure: the role of morphine-6-glucuronide. British Medical Journal, 292:1548-1549, 1986

Raj N, Sehgal A, Hall JE, Sharma A, Murrin KR, Groves ND. Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. Eur J Anaesthesiol. 2004 Dec;21(12):932-7.

Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA. Intrathecal morphine for postoperative analgesia: a randomised, controlled, dose-ranging study after hip and knee arthroplasty. Anesth Analg. 2003 Nov;97(5):1452-7.

Reinoso-Barbero F, Saavedra B, Hervilla S, de Vicente J, Tabares B, Gomez-Criado MS. Lidocaine with fentanyl, compared to morphine, marginally improves postoperative epidural

Relation of plasma morphine concentrations to severity of abrupt withdrawal in morphinedependent responses to alloantigen. Brain Behav Immun 1994; 8:185-203.

Roberts-Thomson IC, Jonsson JR, Frewin DB, Coates GC. Sympathetic activation: a mechanism for morphine induced pain and rises in liver enzymes after cholecystectomy? Gut. 1990 Feb;31(2):217-21. doi: 10.1136/gut.31.2.217. PMID: 2311982; PMCID: PMC1378384.

Romberg R, Olofsen E, Sarton E, den Hartigh J, Taschner PE, Dahan A. Pharmacokinetic-pharmacodynamic modelling of morphine-6-glucuronide-induced analgesia in healthy volunteers: absence of sex differences. Anesthesiology. 2004 Jan;100(1):120-33.

Rose R, Kumar A, Bhattacharya SK. Striatal cholinergic activity during morphine-induced catalepsy in the rat: development of tolerance. Neuroscience Letters 1979; 14:115-8.

Ross DD, Alexander CS. Management of common symptoms in terminally ill patients: Part II. Constipation, delirium and dyspnea. Am Fam Physician. 2001 Sep 15;64(6):1019-26.

Sagratella S, Scotti de Carolis A. In vivo and in vitro epileptogenic effects of the enkephalinergic system. Ann Ist Super Sanità 1993; 29(3): 413-8.

Sarton E, Olofsen E, Romberg R, den Hartigh J, Kest B, Nieuwenhuijs D, Burm A, Teppema

L, Dahan A. Sex differences in morphine analgesia: an experimental study in healthy volunteers. Anesthesiology. 2000 Nov;93(5):1245-54; discussion 6A.

Schechter NL, Berde CB, Yaster M, Maxwell LG Opioid Agonists and Antagonists in Pain in Infants, Children, and Adolescents. Williams & Wilkins, Timothy H. Grayson, 145-171, 1993

Scheufler E, Zetler G. Interactions of caerulein and morphine on gastrointestinal propulsion in the mouse. Naunyn-Schmiedeberg's Arch Pharmacol 1981; 318:66-9.

Schug, S.A., Zech, D. & Grond, S. Adverse Effects of Systemic Opioid Analgesics. Drug-Safety 7, 200–213 (1992). https://doi.org/10.2165/00002018-199207030-00005

Sjögren P & Eriksen J Opioid toxicity. Current Opinion in Anaesthesiology, 7:465-469, 1994

Sjogren P, Thunedborg LP, Christrup L, Hansen SH, Franks J. Is development of hyperalgesia, allodynia and myoclonus related to morphine metabolism during long-term administration? Six case histories. Acta Anaesthesiol Scand. 1998 Oct;42(9):1070-5.

Skarke C, Darimont J, Schmidt H, Geisslinger G, Lötsch J. Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical painmodel in healthy volunteers. Clin Pharmacol Ther. 2003 Jan;73(1):107-21.

Sklar LS, Zalman A Effect of aggregation on morphine lethality in rats. J Pharm Pharmacol 1977; 29:119.

Sloan PA, Mather LE, McLean CF, Rutten AJ, Nation RL, et al. Physiological disposition of i.v. morphine in sheep. Br J Anaesth 1991; 67(4):378-86.

Snyder SH. Opiate Receptors in the Brain. The New England Journal of Medicine, 296(5):266-271, 1977 Spine. 2002 Mar 1;27(5):535-7.

Staahl C, Upton R, Foster DJ, Christrup LL, Kristensen K, Hansen SH, Arendt- Nielsen L, Drewes AM. Pharmacokinetic-pharmacodynamic modeling of morphine and oxycodone concentrations and analgesic effect in a multimodal experimental pain model. J Clin Pharmacol. 2008 May;48(5):619-31.

Stoelting RK. Opioid Agonists and Antagonists. Pharmacology and Physiology in Anaesthetic Practice 1990;70-83

Streltzer J. Pain management in the opioid-dependent patient. Curr Psychiatry Rep. 2001 Dec;3(6):489-96.

Study Code: FIWI.doc/24.11.1994. Tolerance and efficacy of Vendal 200 mg vials during i.v. application using PCA in postoperative patients. Lannacher Heilmittel Ges.m.b.H., Austria, 1994.

Study Code: No.: ILIAS01.XLS. Clinical trial on the application of Vendal 200 mg vials during application using PCA (epidural, intravenous, subcutaneous) and in bolus (intramuscular, intrathecal) in postoperative patients. Lannacher Heilmittel Ges.m.b.H., Austria, 1998.

Suominen PK, Ragg PG, McKinley DF, Frawley G, But WW, Eyres RL. Intrathecal morphine provides effective and safe analgesia in children after cardiac surgery. Acta Anaesthesiol Scand. 2004 Aug;48(7):875-82.

Suzuki T, Hayashi Y, Misawa M. The role of mu1 receptor in physical dependence on morphine using the mu receptor deficient CXBK mouse. Life Sci 1992; 50(12):849-856.

Swain N, Das RK, Paul M. Cytogenetic assay of potential mutagenicity in vivo of two narcotic analgesics. Mutat Res 1980; 78:97-100.

Takzare N, Samizadeh E, Shoar S, Majidi Zolbin M, Naderan M, Lashkari A, Bakhtiarian A. Impacts of morphine addiction on spermatogenesis in rats. Int J Reprod Biomed (Yazd). 2016 May;14(5):303-8.

Tang X, Chen Y, Ran H, Jiang Y, He B, Wang B, Kong S, Wang H. Systemic morphine treatment derails normal uterine receptivity, leading to embryo implantation failure in mice. Biol Reprod. 2015 May;92(5):118.

Tassain V, Attal N, Fletcher D, Brasseur L, Degieux P, Chauvin M, Bouhassira D. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. Pain. 2003 Jul;104(1-2):389-400.

Terajima K, Onodera H, Kobayashi M, Yamanaka H, Ohno T, Konuma S, Ogawa R. Efficacy of intrathecal morphine for analgesia following elective cesarean section: comparison with previous delivery. J Nippon Med Sch. 2003 Aug;70(4):327-33.

Themann P, Havemann U, Kuschinsky K. On the mechanisms of the development of tolerance to the muscular rigidity produced by morphine in rats. Eur J Pharmacol 1986; 129:315-21.

Traudt CM, Tkac I, Ennis KM, Sutton LM, Mammel DM, Rao R. Postnatal morphine administration alters hippocampal development in rats. J Neurosci Res. 2012 Jan;90(1):307-14.

Tsushima H, Mori M, Matsuda T. Antidiuretic effects of morphine microinjected into the hypothalamic supraoptic and paraventricular nuclei in a water-loaded and ethanol-anesthetised rat. Jpn J Pharmacol. 1987 Dec;45(4):449-57. doi: 10.1254/jjp.45.449. PMID: 3444115.

Urban MK, Jules-Elysee K, Urquhart B, Cammisa FP, Boachie-Adjei O. Reduction in postoperative pain after spinal fusion with instrumentation using intrathecal morphine.

van Praag H, Frenk H. The effects of systemic morphine on behavior, EEG in newborn rats.

Vetulani J, Melzacka M, Adamus A, Danek L. Changes in morphine pharmacokinetics in nervous and peripheral tissues following different schedules of administration. Arch Int Pharmacodyn 1983; 265:180-91.

Wang JJ, Ho ST. Acute and chronic opioid tolerance: a pharmacological review. Acta Anaesthesiol Sin 1994; 32:261-7.

White CW, Ward CR, Dombrowski DS, Dunlow LD, et al. Effect of intrathecal morphine on the fate of glucose. Comparison with effects of insulin and xanthan gum in mice. Biochem Pharmacol 1993; 45(2):459-64.

Wiesenfeld-Hallin Z, Södersten P. Spinal opiates affect sexual behaviour in rats. Nature 1984; 309:257-8.

Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. Cochrane Database Syst Rev. 2014 May 29;2014(5):CD011056. doi: 10.1002/14651858.CD011056.pub2. PMID: 24874470; PMCID: PMC6483540.

Wirz S, Klaschik E. Laxative use and efficacy in palliative care of patients with cancer pain and morphine therapy. A retrospective study with special regard to polyethylene glycol. Schmerz. 2003 Aug;17(4):233-9.

Witkin LB, Heubner CF,Galdi F,O´Keefe E, et al. Pharmacology of 2-amino-indane hydrochloride (SU-8629): A potent non-narcotic analgesic. Summit New Jersey 1961; 133:400-8.

Wu CL, Tella P, Staats PS, Vaslav R, Kazim DA, Wesselmann U, Raja SN. Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomised double-blind, active placebo-controlled, crossover trial. Anesthesiology. 2002 Apr;96(4):841-8.

Zagon IS, Mc Laughlin PJ. Morphine and brain growth retardation in the rat. Pharmacology 1977; 15:276-82.

Zimmerberg B, Charap AD, Glick SD. Behavioural effects of in utero administration of morphine.