CBG MEB

Public Assessment Report

Scientific discussion

Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for infusion, and Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for injection

(morphine hydrochloride)

NL/H/3729/001-006/DC

Date: 12 June 2018

This module reflects the scientific discussion for the approval of Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for infusion and Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for injection. The procedure was finalised on 20 April 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
M3G	Morphine-3-Glucuronide
M6G	Morphine-6-Glucuronide
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for infusion and Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for injection from Eurocept International B.V.

The product is indicated for the treatment of severe acute pain, cancer pain and breakthrough cancer pain.

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of morphine hydrochloride solution for injection/solution for infusion. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. “Medicinal use” does not exclusively mean “use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

The concerned member states (CMS) involved in this procedure were Belgium, Germany, Denmark, Finland, Luxembourg, Norway and Sweden.

The application is based on article 10(a) of Directive 2001/83/EC, a so called bibliographic application.

II. QUALITY ASPECTS

II.1 Introduction

Sendolor is a clear and (almost) colourless solution for injection/infusion. The pH is 3.0-4.5 and the osmolality is 270-330 mOsm/kg.

- Sendolor 1 mg/ml, solution for infusion:

Each ml of solution for infusion contains 1 mg morphine hydrochloride trihydrate.
1 bag with 100 ml solution for infusion contains 100 mg morphine hydrochloride trihydrate equivalent to 75,92 mg morphine.

- Sendolor 10 mg/ml, solution for infusion:

Each ml of solution for infusion contains 10 mg morphine hydrochloride trihydrate.
1 bag with 100 ml solution for infusion contains 1000 mg morphine hydrochloride trihydrate equivalent to 759 mg morphine.

- Sendolor 20 mg/ml, solution for infusion:

Each ml of solution for infusion contains 20 mg morphine hydrochloride trihydrate.
1 bag with 100 ml solution for infusion contains 2000 mg morphine hydrochloride trihydrate equivalent to 1518,4 mg morphine.

- Sendolor 1 mg/ml, solution for injection:

Each ml of solution for injection contains 1 mg morphine hydrochloride trihydrate.
1 ampoule with 10 ml solution for injection contains 10 mg morphine hydrochloride trihydrate equivalent to 7,59 mg morphine.

- Sendolor 10 mg/ml, solution for injection:

Each ml of solution for injection contains 10 mg morphine hydrochloride trihydrate.
1 ampoule with 1 ml solution for injection contains 10 mg morphine hydrochloride trihydrate equivalent to 7,59 mg morphine.

- Sendolor 20 mg/ml, solution for injection:

Each ml of solution for injection contains 20 mg morphine hydrochloride trihydrate.
1 ampoule with 1 ml solution for injection contains 20 mg morphine hydrochloride trihydrate equivalent to 15,18 mg morphine.

The solution for infusion is packed in:

- polypropylene/polyolephine bags with two tubes, one twist-off and the other either with a female Luer lock with bi-directional valve or with an injection site. All bags are overwrapped in outer pouches consisting of multi-layer co-extruded films made of PET (polyester)/OPA (polyamide)/Aluminum/PP. Between the bag and the overwrapping there is an oxygen absorbing sachet.

The solution for injection is packed in:

- glass type I ampoules

The excipients of the solution for infusion are sodium chloride, hydrochloric acid (for pH adjustment) and water for injection.
The excipients of the solution for injection are sodium chloride and water for injection.

II.2 Drug Substance

The active substance is morphine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Morphine hydrochloride is a white or almost white, crystalline powder, colourless silky needles or cubical masses and efflorescent in a dry atmosphere. The drug substance is soluble in water, slightly soluble in ethanol (96%) but practically insoluble in toluene. Morphine hydrochloride is chiral, polymorphism issues are not relevant as the drug product concerns a solution. A copy of the Ph. Eur. certificate of suitability of the drug substance manufacturer has been provided by the drug product manufacturer.

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.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 18 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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. Compatibility between the product and the plastic infusion bags has been evaluated. Additionally, the potential formulation quality aspects (potential water loss through the bag, oxygen content, product pH, osmolality) have been discussed. The pharmaceutical development of the product has generally been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The process consists of weighing, mixing, adjustment of volume, filtration, filling, steam- sterilization in the intended packaging, and packaging in the secondary packaging (carton box). Process validation data on the product have been presented for three pilot scale batches per strength and presentation in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All excipients comply with their current Ph. Eur. monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for characters, identifications, extractable volume, pH of the solution, osmolality, related substances and degradation products, impurities, active substance content, sterility, particulate matter and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from at least two pilot or production scale batches ampoules and bags of every strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for at least two pilot scale batches ampoules and bags of every strength stored at 25°C/40% RH (36 or 60 months), 30°C/65% RH (36 or 60 months) and 40°C/not more than 25% RH (6 months). The conditions were in accordance with applicable European guidelines.
The MAH has adequately justified the absence of a photo stability study. As the morphine hydrochloride is light sensitive the proposed storage conditions are acceptable.
The proposed shelf-life of 24 months and storage conditions “must be stored in the commercial packaging protected from light” for ampoules and the proposed shelf-life of 36 months and storage conditions “must be stored in their overwrapping” for bags are regarded acceptable.

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 member states consider that Sendolor 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 Ecotoxicity/environmental risk assessment (ERA)

Medicinal product Applications submitted under article 10a of Directive 2001/83, well-established use, will substitute products already on the market with the same active substance and the same indication. Sales data from the past four years of total morphine and parenteral morphine in The Netherlands and the Concerned Member States suggest that marketing authorisation of Sendolor will not lead to a significant increased use of morphine in the RMS and in the Concerned Member States.

III.2 Discussion on the non-clinical aspects

Morphine is a well-known an opiate agonist. The nonclinical overview adequately reviewed public literature on pharmacology, pharmacokinetics and toxicology of morphine. No additional nonclinical studies are needed. Morphine is an opioid analgesic with agonist activity mainly at μ-opioid receptors and perhaps at κ and δ receptors. It acts mainly on the central nervous system and smooth muscle. Although morphine is mainly a central nervous system depressant, it has some central stimulant actions which result in nausea, vomiting and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts. Non-clinical data on the toxicological properties of morphine hydrochloride reveal no special hazard for humans in addition to what is known from clinical experience.

IV. CLINICAL ASPECTS

IV.1 Introduction

Morphine hydrochloride is a well-known active substance with established efficacy and tolerability. The dossier is based on well-established use of the active substance. The MAH submitted a clinical overview for the justification of the proposed indications and posology. Sufficient literature references were provided.

IV.2 Pharmacokinetics

The products under consideration contain the active morphine hydrochloride and the well-known excipients sodium chloride and water for injections. The medical use of morphine hydrochloride as a solution for injection/infusion is well established. The excipients in the product under consideration are widely used in the manufacturing of parenteral pharmaceutical products and do not interact with the drug substance (e.g. complex formation), or otherwise affect the disposition of the drug substance. Differences in quantity of the excipients will not affect the pharmacokinetics of the active substance. The product does not contain preservatives.

Absorption

Subcutaneous and intramuscular administration

After subcutaneous or intramuscular injection morphine is readily absorbed into the blood. The dose-concentration relationship is linear over a wide range of doses (20-750 mg/day), and the dose can be increased without causing accumulation. Factors influencing include variation in blood pressure and tissue perfusion, site of injection, pH of injection site, and drug lipophilicity. intramuscular absorption is rapid (absorption t/2-8 min), and the peak occurs at 10-20. Systemic bioavailability is essentially complete. Since the pharmacokinetics of subcutaneous morphine are similar to those of intramuscular morphine, subcutaneous morphine is a suitable, alternative parenteral route. Peak plasma concentration occurs at ~15 min, and plasma levels equivalent to those obtained with the intravenous (IV) route can be.

Epidural and intrathecal administration

Morphine injected into the epidural space is rapidly absorbed into the general circulation. Absorption is so fast that the plasma concentration-time profiles closely resemble those obtained after intramuscular or IV administration.

Peak plasma concentrations of 5 to 50 ng/ml are achieved within 10 to 15 minutes after epidural injection of 2 to 14 mg of morphine. The range of maximum concentration (C_{max}) after commonly used therapeutic doses of 2 to 5 mg is from 5 to 31 ng/ml. Plasma concentrations decline in a multiexponential fashion; at least two distinct phases can be observed in the first 8 to 10 hours.

Intrathecally administered morphine appears in the general circulation much more slowly than does epidurally administered morphine. Additionally, a lower C_{max}, a later onset of peak concentration, and even a later appearance of morphine-glucuronide in blood compared with those seen with epidural and intramuscular administration achieved in the cerebrospinal fluid surrounding the injection site, has been found. The cerebrospinal fluid levels of morphine after intrathecal administration of 0.25 to 0.5 mg are still higher than those seen after epidural administration of a tenfold larger dose.

Distribution
Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the cerebrospinal fluid as have its highly polar metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Morphine diffuses across the placenta and traces also appear in breast milk and sweat. About 35% is protein bound.

Elimination
The mean total urinary recovery of morphine, M6G, and M3G is about 75% of the dose. It is impossible to determine a relationship between morphine clearance, M3G, M6G, and creatinine owing to interindividual differences in tubular secretion and reabsorption of morphine. The elimination half-life of morphine is approximately 2h and is independent of route of administration or formulation. Rectal pharmacokinetics varies according to the anatomical location of the suppository, because of differences between portal (inferior and middle hemorrhoidal vein) and systemic (superior hemorrhoidal vein) venous. The inferior and middle hemorrhoidal arteries bypass splanchnic blood flow and hepatic clearance, resulting in higher morphine levels but reduced M3G and M6G. However, there is extensive anatomosis between the two systems, producing only a partial hepatic bypass effect. After rectal administration the area under the curve (AUC) is greater and less M3G and M6G are produced. Rectal administration produces the same level of analgesia as oral morphine.

Metabolism
The liver is the principal site of morphine glucuronidation. There is a minor contribution (30%) to glucuronidation from the kidneys. The UDP-glucuronosyl-transferase isoenzyme UGT2B7, found on chromosome 4, is the main morphine-metabolising enzyme. Three major metabolites are produced: normorphine, M3G, and M6G. M3G is devoid of analgesic activity, and it does not antagonise analgesic or respiratory depressant effects of morphine or M6G. M6G is a hydrophilic metabolite that is 10-60 times as potent as morphine. Normorphine-2 glucuronide elicits central nervous system excitation in a similar way to M3G.

Special populations
Impaired renal function
Morphine is one of the opioids whose dosing is least affected by hepatic failure but is greatly affected by renal failure. A significant relationship has not been found between the renal clearance of morphine, M3G or M6G, and creatinine clearance. This is probably due to the confounding influences of concomitant drug therapy on the renal clearance of morphine and its metabolites and the narrow range of creatinine clearance values, many of which were normal.
In a population of intensive care patients with very diverse renal function, significant relationships were found between the creatinine clearance and renal clearance of morphine, M3G and M6G. The results indicate the importance of renal function in determining the renal clearances and plasma concentrations of M3G and M6G during IV infusion with morphine in intensive-care patients. The authors stated that it is possible that steady-state concentrations of morphine may not have been achieved in the patients infused for the shorter periods. Considering the limited number of patients, varying renal impairment in these patients and limitation of steady-state status, a definite conclusion can not be drawn from the study.
Reports on the accumulation of morphine are conflicting. In general, the reports concur as to the accumulation of the active metabolite M6G in renal impairment. A decrease in renal clearance can lead to high plasma concentrations, which can lead to serious adverse events and can be fatal.

Impaired hepatic function
Although an increased exposure, reduced clearance and an extended half-life of morphine was reported in patients with cirrhosis and liver cancer, the reported data on the effect of hepatic impairment on morphine are not robust and not always in concordance. There are no reported systematic studies done on the different stages of hepatic impairment. In general, the available evidence suggests that morphine metabolism is impaired in patients with severe chronic liver disease (i.e. cirrhosis and liver cancer). This is in line with the hepatic metabolism of morphine. Furthermore, the available literature data indicate that oral administration exert a stronger influence on the pharmacokinetics of morphine in comparison with IV administration, which can be explained by a reduction in first-pass effect. However, no data/information are available on mild and moderate hepatic impairment.

Elderly
Elderly individuals have a delayed clearance of morphine metabolites owing to reduced renal clearance. The volume of distribution is smaller, but the time to maximum concentrations is unaltered.

Neonates, children and adolescents
Neonates have a reduced capacity to metabolise morphine. Adequate warnings have been added to the SmPC that children, and particular neonates, may therefore be at increased risk of venticulary depression. Recent literature and PK modeling indicate that a 50% reduction of the regular 0.05 mg/kg dose to 0.025 mg/kg led to adequate analgesia in the youngest age group of term neonates with a post-natal age of 10 days in postoperative pain. The starting dose for neonates has been adapted accordingly.

Older children are likely to have significantly lower plasma morphine and metabolite concentrations than adults when given an equivalent dose for weight. This may reflect reduced bioavailability, increased clearance or a larger volume of distribution.

Interactions
Phenothiazines, including promethazine and chlorpromazine, inter-ere with morphine metabolism. Tricyclics also inhibit morphine glucuronidation; nortriptyline noncompetitively and amitriptyline competitively. Carbamazepine, phenobarbital, phenytoin and rifampicin induce UDP-glucuronyl transferase activity and may accelerate the clearance of morphine. However, the sum effect of combining antiseizure medications with morphine may be significant sedation.
Benzodiazepines, particularly those that are glucuronidated (such as lorazepam), may competitively interfere with morphine glucuronidation. Cimetidine inhibits n-dealkylation of morphine, and ranitidine alters glucuronidation in favor of M6G, but both are of questionable clinical significance. Kaolin decreases gastrointestinal absorption. Rifampicin accelerates glucuronidation, reducing AUC and the maximum morphine, M3G, and M6G concentrations. Cisapride and metoclopramide accelerate absorption, and metoclopramide increases sedation when sustained-release morphine is co-administered. In animal studies metoclopramide reduces acute morphine tolerance.
Interactions of morphine with antineoplastic agents have never been described, apart from opioids sharing CYP3A4 or CYP2D6 metabolism. Insufficient effectiveness of serotonin-antagonists has been reported in patients with cisplatin-induced emesis who were receiving morphine, possibly due to the reinforcement of emetic mechanisms of the two drugs. Pharmacodynamic interactions have been described in the literature between gabapentin and morphine. In general, interactions are expected to be similar between adults ad children.

IV.3 Pharmacodynamics

Similar to the endogeneous opioid peptides, morphine is thought to dose-proportionally activate several opioid receptors most importantly μ (mu, OP3), but probably also κ (kappa, OP2), and δ (delta, OP1) receptors mediating analgesia.
Analgesic effects of morphine are directly associated with its antagonism of the opioid receptors, most importantly the μ-receptor. Tolerance and both physical and psychological dependence may develop in particular with prolonged use, through several pathophysiological pathways. Some older publications (1980, 1986) are referred to in support of the hypothesis that risk of dependence is low in the clinical treatment of pain.
Apart from analgesic effects, μ-receptors are postulated to mediate respiratory depression, miosis, reduced gastrointestinal motility, and euphoria. K-receptors may induce miosis and respiratory depression, dysphoria and psychotomimetic effects. Morphine is a potent central nervous system-depressant but also exhibits stimulant actions including nausea and vomiting, and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts.

IV.4 Clinical efficacy

Efficacy of IV morphine in the treatment of severe pain in several medical conditions is considered well established and well characterised within the approved recommendations for use. The IV route of administration is considered particularly effective.

The proposed indications of severe acute pain, cancer pain and cancer breakthrough pain are supported, and in line with the EMA guideline on pain.

As far as known, only oro transmucosal fentanyl citrate and intranasal fentanyl are registered for the treatment of breakthrough cancer pain via centralised procedures in Europe. IV morphine was superior to oral transmucosal fentanyl citrate with faster onset of effect in a randomised cross-over trial in 25 patients with breakthrough cancer pain, despite optimised background therapy with opioids. The dose was further established is several uncontrolled studies. E.g. in a uncontrolled cohort study of 945 episodes of breakthrough pain, a similar dosing regimen (20% of total daily equivalent oral morphine dose) did not result in life-threatening adverse effects, including older patients or patients with high baseline opioid use. The mean pain intensity decreased from 7.2 to 2.7, on a numerical scale of 10 points after 15 minutes IV morphine may be an useful alternative for oro transmucosal fentanyl citrate products for those –terminal- cancer patients with IV access, who cannot tolerate oromucosal fentanyl citrate, e.g. because of oral candidiasis. European palliative care guidelines also recommend IV opioids for acute cancer pain. Altogether, the benefit/risk is considered positive for this indication.

IV.5 Clinical safety

Adverse effects of morphine are well-characterised, dose-dependent and most depressant effects are to some extent counteracted by the pain symptoms that are focus of treatment. The same is postulated to apply for the risk of abuse and dependence.
Adverse effects include nausea, vomiting, constipation, drowsiness, and confusion and are dose-dependent. Other frequent undesirable effects include dry mouth, dizziness, sweating, facial flushing, headache, vertigo, bradycardia, tachycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, decreased libido or potency, hallucinations, and miosis.
Urinary retention may occur and ureteric or biliary spasm including liver damage, raised intracranial pressure or muscle rigidity in particular with high doses. The euphoric effect is associated with abuse potential. Respiratory depression may occur, low blood pressure and bradycardia. Naloxone is effective in alleviating toxic effects including shock and coma.

IV.6 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 Sendolor.

- 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 - Use in patients with hepatic impairment
Missing information	- Use in pregnancy and breastfeeding

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

IV.7 Discussion on the clinical aspects

Morphine hydrochloride has been used and is registered for the requested indications in the RMS and the CMS countries for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of morphine hydrochloride in the proposed indications can be considered well-established with demonstrated efficacy. The proposed dose for both indications is in line with current recommendations. On the basis thereof, the efficacy of Sendolor can be considered acceptable.

The safety profile of morphine hydrochloride in the proposed indications can be considered well-established and acceptable. The proposed posology for both indications is in line with current recommendations. The adverse events of morphine hydrochloride are well characterised and adequately covered by the SmPC's of currently available morphine hydrochloride products.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for infusion and Sendolor 1 mg/ml, 10 mg/ml and 20 mg/ml, solution for injection have a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the proposed indication in the treatment of severe acute pain, cancer pain and breakthrough cancer pain, as well as the proposed posology are in line with current morphine hydrochloride use and recommendations in the RMS and CMS countries, in which morphine hydrochloride has been registered for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of morphine hydrochloride in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Sendolor with the reference product, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 20 April 2017.

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
NL/H/3729/1-6/IA/001	Replacement or addition of a manufacturer responsible for importation and/or batch release; not including batch control/testing	N	11-03-2018	Approval	-
NL/H/3729/1-6/IB/002	Add a description of the second stopper configuration, an injection site, to the SmPC, section 6.5	Y	04-04-2018	Approval	-
NL/H/3729/1-6/IB/003	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph; new certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free	N	10-05-2018	Approval	-
NL/H/3729/1-6/1B/004/G	To correct the pharmaceutical form of Sendolor from 'solution for injection/infusion' to: 'solution for injection' for the ampoules; and 'solution for infusion' for the bags	Y	24-05-2018	Approval	-