COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Esketiv 5 mg/ml and 25 mg/ml, solution for injection

(esketamine hydrochloride)

NL/H/4077/001-002/DC

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This module reflects the scientific discussion for the approval of Esketiv 5 mg/ml and 25 mg/ml, solution for injection. The procedure was finalised at 5 June 2018. 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
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 Esketiv 5 mg/ml and 25 mg/ml, solution for injection, from Eurocept International B.V.

The product is an anaesthetic and is indicated for:

- for the induction and maintenance of general anaesthesia and as a supplement to other anaesthetics.
- in short-term diagnostic procedures and small surgical procedures that do not require muscle relaxation

The product is indicated in children and in adults.

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

Esketamine hydrochloride is a well-established anaesthetic and has been used in the community for more than 40 years. In the Netherlands Ketanest-S 5 mg/ml and 25 mg/ml, solution for injection are registered via a national procedure by PfizerB.V. and marketed since 19 January 1999.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of esketamine hydrochloride. 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 Austria, Belgium, Germany, Finland, France, Norway, Poland, Sweden and Slovenia.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Esketiv is a clear and colourless solution for injection.

Each ml of Esketiv 5 mg/ml solution for injection contains esketamine hydrochloride equivalent to 5 mg esketamine. 1 ampoule of 5 ml contains esketamine hydrochloride equivalent to 25 mg esketamine. 1 ampoule of 20 ml contains esketamine hydrochloride equivalent to 100 mg esketamine.

Each ml of Esketiv 25 mg/ml solution for injection contains esketamine hydrochloride equivalent to 25 mg esketamine. 1 ampoule of 10 ml contains esketamine hydrochloride equivalent to 250 mg esketamine.

The solution for injection is packed in glass type I ampoules.

The excipients are: sodium chloride, hydrochloride acid (for pH adjustment) and water for injections.

II.2 Drug Substance

The active substance is esketamine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder. Esketamine hydrochloride is soluble in alcohol and ethanol and freely soluble in methanol and water. The active substance has a chiral centre and the s-configuration is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the MAH or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
Esketamine hydrochloride is synthesised in 6 steps from the starting material R,S-Ketamine hydrochloride, which is covered by a valid CEP by the same manufacturer. The active substance has been adequately characterised and acceptable specifications have been adopted for all materials.

Quality control of drug substance
The active substance specification has been established in-house by the MAH based on the Ph.Eur. monograph. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for 11 full scaled batches stored at 25°C/60% RH (varying from 3 to 60 months) and 40°C/75% RH (varying from 3 to 6 months). No significant changes or out of specification results in any of the parameters monitored are observed at either long-term or accelerated conditions. A retest period of 5 years with no additional storage conditions is accepted.

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. For the pharmaceutical development of the proposed finished product reference to literature on registered product containing ketamine and esketamine is made. According to the well-established use MA-procedure, the MAH has provided detailed comparisons of cited registered EU products with the proposed drug product in order to justify that that the compositions and characteristics of the cited products are comparable to those of the proposed product.
With regard to the pharmaceutical development for the paediatric population the MAH has provided a detailed comparison of the cited registered EU products with the proposed drug product and therefore it can be concluded that no safety issues for the paediatric population are expected.

Manufacturing process
The manufacturing process is well presented in a flow chart also in the narrative description. It has been validated according to relevant European guidelines. The process can be considered standard. Process validation data on the product have been presented for an appropriate amount of batches in accordance with the relevant European guidelines.

Control of excipients
All excipients are described in the Ph. Eur. and are in compliance with the 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, identification, extractable volume, pH, osmolality, related substances, degradation products, impurities, esketamine 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 seven batches 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 seven (2 x 5 mg/ml in 5 ml, 2 x 5 mg/ml in 20 ml and 3 x 25 mg/ ml in 10 ml) batches stored at 40°C, 30°C, 25°C and 5°C (up to 36 months). The batches were stored in accordance with applicable European guidelines. Photo stability tests showed that the product is sensitive to light. On basis of the data provided, a shelf life could be granted of 24 months with the storage condition: "store in the original package protected from light".

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 Esketiv 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 Introduction

For the current application procedure, no new non-clinical studies have been performed. A non clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional non clinical data. Below is an assessment of the provided literature to establish efficacy and safety.

III.2 Pharmacology

Esketamine is a fast-acting anaesthetic and analgesic. The analgesic effect occurs at doses lower than those required for the anaesthesia and lasts longer. These pharmacological effects are attributed to the blockade of the N-methyl-D-aspartate (NMDA) receptors by esketamine. The ketamine-racemate consists of the enantiomers S-ketamine (esketamine) and (R)-ketamine. The efficacy of esketamine is approximately twice as large compared to the ketamine-racemate at the same dosage.

Considerable literature data has been submitted to support that esketamine modulates non-NMDA receptors as well. Esketamine may exert an antidepressant effect via modulation of

dopamine release, mTOR activation, BDNF translation, GSK-3 inhibition, and modulation of nACh receptors. It had an anti-inflammatory effect via suppression of LPS-induced TNF-α, IL-6, and IL-8 production. Racemic ketamine has been reported to inhibit neutrophil adhesion to the endothelium *in vitro* and to modulate energy metabolism pathways such as the citrate cycle; glycine, serine and threonine metabolism; pyrimidine metabolism; modulation of the pentose phosphate pathway; and modulation of glycolysis and gluconeogenesis. An antineoplastic role for racemic ketamine has also been suggested, but the data is limited and conflicting. Differences between esketamine, R-ketamine and racemic ketamine may influence secondary pharmacodynamics, but have been discussed enough to allow for a meaningful non-clinical assessment.
Formal safety pharmacology studies according to ICH S7A/B have not been performed. Nevertheless, the safety pharmacology of esketamine has been sufficiently addressed and is well understood, also because of extensive clinical experience. Esketamine has a profound effect on the central nervous system and behaviour, which is derived from its primary pharmacology. Effects in juvenile animals are difficult to interpret with regard to its clinical relevance. For ketamine, and by extension esketamine, this results in a potential for dependence and abuse in both animals and humans. No data on pharmacodynamic drug interactions have been submitted. The literature overview presents data derived from experiments with ketamine, esketamine and R-ketamine. While differences in potency exist between the isoforms and the mixture, the data are sufficient to allow a meaningful assessment of the non-clinical pharmacodynamics of esketamine. The primary, secondary and safety pharmacology have been adequately discussed based on available literature.

III.3 Pharmacokinetics

The submitted literature data are adequate to assess the non-clinical absorption, distribution, metabolism and elimination of Esketamine. Ketamine is rapidly systemically absorbed after an intraperitoneal injection with C_{max} after 0.25 hours. Esketamine has a short half-life: exposure decreases rapidly and below lower limit of quantification after 4 and 8 hours in mice and rats, respectively. Plasma protein binding is low. There is no enantio-selectivity in distribution. Therefore, data on racemic mixtures, R- and S-ketamine can be used equally. After iv administration, ketamine rapidly distributes to central nervous system and brain. Brain : plasma ratios favour brain, suggesting accumulation. It has been proposed that this is driven by active transport of ketamine into the central nervous system. S-ketamine is more completely and more rapidly transformed when it is administered alone, compared to when it is present in a racemic mixture, suggesting competition of the enantiomers. Ketamine is metabolized in liver, and 2 metabolic pathways of ketamine with its main metabolites have been proposed in literature. Relevant CYPs and/or metabolic enzymes are discussed in the chapter on pharmacokinetic drug-drug interactions. Given the extensive clinical experience with S-ketamine, this overview on non-clinical metabolism is considered sufficient. S-ketamine has a significantly higher systemic clearance when dosed alone than in the racemate, suggesting inhibition of S-ketamine clearance by the R-ketamine. The available literature suggests that CYP3A, CYP2C9 and CYP2B6 are key enzymes in the metabolism of ketamine and where interactions with other drugs can occur.

III.4 Toxicology

Most single dose toxicity data are at lethal doses and not informative for safety assessment. In humans, the lowest recommended i.v. dose to induce anaesthesia is 1 mg/kg, which is well below the lethal non-clinical doses that were used. No data are available for esketamine. However, it is not expected that different toxic results would be obtained with the enantiomer at very high doses.
Central nervous system and brain is a target organ of toxicity after prolonged exposure to ketamine. In particular, hippocampal volume loss was noted, which is associated with depression. In contrast, repeated ketamine infusions induced rapid and long lasting antidepressant effects in patients with treatment-resistant depression. Neurodegeneration and decreases of parvalbumin (PV)-positive cells in the brain were observed, which is associated with schizophrenia and psychosis. Administration of esketamine appears to result in more pronounced effects compared to R-ketamine, potentially due to the higher affinity in binding to NMDA receptors of esketamine. Finally, adrenal gland and pancreas are target organs of toxicity, with decreases in localisation of cells expressing enzymes needed to produce catecholamines and decreases in the number of large β-islet cells.
Given the short duration of treatment and the long clinical experience with esketamine, the provided non-clinical literature overview is sufficient.

The carcinogenic potential of esketamine has been discussed on the basis of published data. These data show that esketamine is unlikely to possess genotoxic properties at the clinical indicated doses up to 4 mg/kg bw. It was shown that

- Ketamine was not mutagenic in bacterial mutagenicity tests (Waskall, 1978).
- Ketamine was clastogenic in an in-vitro sister chromatid exchange test in CHO cells, but the effects were weak at the tested concentrations of 1.19, 2.38 and 3.66 mg/l (i.e. less than a doubling of control values) and thus the relevance of this finding is questionable (Adhvaryu et al., 1986).
- Unpublished data (submitted to the German Federal Institute for Drugs and Medical Devices as part of an application for a marketing authorization) from genotoxicity testing with the S(+) enantiomer of ketamine in a standard battery of validated *in vitro* and *in vivo* tests did not reveal any evidence for a genotoxic potential (WHO 2005). A report from the EMCDDA indicated that for that application, the genotoxic potential of S-ketamine was evaluated in the following tests (EMCDDA 2002): (1) a test for gene mutation in bacteria, (2) an in-vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay and (3) an in-vivo test for chromosomal damage using rodent hematopoietic cells.

A study that was not discussed by the MAH is in an in-vivo assay for DNA damage (comet assay) in mice (Leffa et al. 2016). In that study, the potential of ketamine to induce DNA damage was evaluated at three doses that are commonly used for anaesthesia of laboratory animals: 80, 100, and 140 mg/kg. It was shown that only the highest dose of 140 mg/kg ketamine was capable of causing genotoxicity in the blood cells and in the brain cortex. This genotoxic effect is not relevant at the indicated clinical dose up to 4 mg/kg.
Carcinogenicity studies are not required, in view of the short-term use.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The product is intended as a substitute for other esketamine hydrochloride products on the market. The approval of this product will not result in an increase in the total quantity of esketamine hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

III.6 Discussion on the non-clinical aspects

The application for this product is based on well-established use. This is endorsed, since esketamine hydrochloride has been registered for this indication for a long time and the dose is not increased. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Esketamine hydrochloride 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 member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Absorption

Two studies investigate the pharmacokinetics of S-ketamine in humans (White et al., 1985; Geisslinger et al., 1993). White et al (1985) evaluated the pharmacokinetic effects of S-ketamine (140 ± 21 mg), R-ketamine (429 ± 37 mg) and the racemate (275 ± 25 mg) after IV administration in healthy volunteers. This study saw no difference in pharmacokinetic parameters between the three drugs. This was further observed by Geisslinger et al (1993), who have shown that the parameters of S-ketamine were similar to those of R-ketamine after administration of the racemate to patients undergoing surgery (1 mg/kg isomer specific and 2 mg/kg for the racemate). After the administration of the pure S-enantiomer, this study also observed that no R-ketamine was detected, suggesting that no inversion occurred after S-ketamine. After administration of the racemic compound, the plasma concentrations of R- and S-ketamine were similar.

More recently, Rotroff et al (2016) have a observed C_{max} of 0.5 mg/kg using racemic ketamine, which was comparable to the observed C_{max} of esketamine when patients were dosed with 0.4 mg/kg based on the assumption that esketamine is ~3 times more potent than R-ketamine. Using a sub-anaesthetic dose (0.2 mg/kg), the mean C_{max} of esketamine treatment was lower than the C_{max} of 0.5 mg/kg racemic ketamine.

Distribution

Racemic ketamine is rapidly distributed to highly perfused tissues, including the brain, to achieve levels four to five times those in plasma (Sigermans et al., 2009; White et al., 1982; White et al., 1975). Ketamine has a high lipid solubility and low plasma protein binding (12%), which facilitates rapid transfer across the blood–brain barrier.
S-ketamine has a central volume of 9.15 L and is rapidly distributed to the peripheral compartment with a distribution rate constant of k13s of 64.3 h-1. Fanta et al (2015) modelled the volume of distribution of S-ketamine to be 420 L/70kg.

Metabolism

At therapeutic concentrations, CYP2B6 is the major CYP isoform catalysing S-ketamine demethylation to norketamine (Yanagihara et al., 2001; Hijazi et al., 2002), which is considered as an active metabolite (Leung et al., 1986; Herd et al., 2007; Holtman et al., 2008). S-Ketamine and S-norketamine are further transformed into two diasteromeric hydroxyketamine and six diastereomeric hydroxynorketamine metabolites and dehydronorketamine (Trevor et al., 1983; Portmann et al., 2010).

Elimination

Ketamine has a high clearance and after the administration of racemate a statistically significantly smaller clearance and a smaller volume of distribution at steady state compared with S-ketamine (Zsigmond et al., 1980). The volume of distribution and clearance for S-ketamine is between 9-14 % greater than those for R-ketamine (Engelhardt et al., 1997). S-ketamine clearance was significantly higher (26.3 mL/kg/min) in comparison with racemic ketamine (14.8 mL/kg/min) (Ihmsen et al., 2001). The clearance of S-ketamine was lesser (18.5 mL/kg/min) in the racemate than when it was given as a pure isomer, demonstrating that R-ketamine inhibits the clearance of S-ketamine.
A study conducted by Sigermans et al (2009) suggested that gender may also impact the elimination of S-ketamine. Sex differences were observed, with a 20% greater elimination clearance of S-ketamine and S-norketamine in women resulting in higher peak plasma concentrations in men. The cause for the difference in clearance between the sexes remains unknown, but it may be related to sex differences in drug plasma protein binding, liver perfusion, and/or activity of the CYP3A4 isoform (HIjazi et al., 2002).

Pharmacokinetics in paediatric subjects

Weber et al (2004) have compared plasma concentrations of S-ketamine (2 mg/kg) and its main metabolite s-norketamine after nasal and IV administration in preschool children (20 children, aged 1-7 years). Following IV-injection the mean S-ketamine plasma concentrations were significantly higher than after nasal administration throughout the study period (C_{max} IV= 1860 ± 883 ng/mL, 3 minutes; C_{max} IN = 335 ± 172 ng/mL; 18 minutes). Intravenous S-

ketamine C_{max} value is a value that has been reported to be associated with surgical anesthesia in adults (Laven et al., 1993). However, 60 min after drug administration plasma concentrations had fallen to values below the adult sedation threshold.

Drug interactions

As indicated by the MAH, S-ketamine undergoes extensive oxidative metabolism by CYP3A, it is prone to pharmacokinetic drug interactions. There are no systematic *in vivo* studies with ketamine and drugs that induce CYP3A enzyme, however three clinical studies have investigated drug interactions in St Johns Wort, rifampicin and grapefruit juice (Peltoniemi et al., 2012a, b and c). After two weeks pre-treatment with St John's wort decreased mean $AUC_{0-\infty}$ of ketamine by 58% and C_{max} by 66% and reduced its t½ after oral administration. The maximum decrease in exposure of ketamine was 4.8-fold between the phases. The decreases in the mean $AUC_{0-\infty}$ and C_{max} of the CYP3A-mediated metabolite norketamine were 23% and 18%. Rifampicin affected the pharmacokinetics of both intravenous and oral S-ketamine and its N-demethylated metabolite, norketamine. The plasma concentrations of S-ketamine and S-norketamine were greatly decreased, particularly after oral administration. Rifampicin decreased the mean $AUC_{0-\infty}$ of intravenous S-ketamine by 14%, increased its mean plasma clearance by 19% and decreased its t½ from 5.9 h to 5.1 h. Furthermore, rifampicin had significant effects on norketamine concentrations after intravenous S-ketamine. Grapefruit juice was shown to increase the $AUC_{0-\infty}$ of oral ketamine by 3.0-fold. The C_{max} of ketamine was increased 2.1-fold following grapefruit juice administration. The elimination half-life of orally administrated S-ketamine was prolonged 1.2 fold from 4.9 to 5.7 h. In addition, grapefruit juice increased $AUC_{0-\infty}$ of norketamine by 1.2-fold but C_{max} and t_{max} of norketamine remained unchanged. The metabolite-to-parent drug AUC ratio was significantly decreased during the grapefruit phase as compared to the water phase.

IV.3 Pharmacodynamics

Since the 1980s, ketamine's mechanism of action has been considered to be mainly a noncompetitive antagonist of the NMDA receptor [Lodge et al (1982), Chizh et al (2013) in Gao et al (2016)]. It was discovered in later research that ketamine also targets other receptors, such as α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid receptors, and has additional acts as an agonist of the sigma 1 receptor [Chizh et al (2013) in Gao et al (2016)]. The dissociated effect is related to the high degree of phencyclidine site occupancy of NMDA receptors [Chizh et al (2013) in Gao et al (2016)]. Thus, S-ketamine provides a dissociative anesthetic state by blocking the connections between the limbic system and thalamus, while it provides an analgesic and antihyperalgesic effect when used in subanaesthetic doses. The latter is mainly attributed to antagonism of the NMDA receptor, an excitatory inotropic glutamate receptor located in the central as well as the peripheral nervous system [Juel et al (2015)].

Mechanism of action

S-ketamine non-competitively antagonizes the NMDA receptor by at least two distinct mechanisms: as a channel blocker, binding to a site within the channel pore to occlude the

channel and reduce mean open time, and through an allosteric mechanism to decrease channel opening frequency [Orser et al., 1997) in Li &Vlisides (2016)].

Primary pharmacology

S-ketamine provides a dissociative anesthetic state by blocking the connections between the limbic system and thalamus, while it provides an analgesic and antihyperalgesic effect when used in subanaesthetic doses. The latter is mainly attributed to antagonism of the NMDA receptor, an excitatory inotropic glutamate receptor located in the central as well as the peripheral nervous system [Juel et al (2015)]. NMDA receptor antagonists like ketamine facilitate glutamatergic neurotransmission through blocking the NMDA receptors resulting in increased glutamate in the frontal lobe [Deakin et al (2008) in Järventausta et al (2015)].

Glutamate is the most common excitatory neurotransmitter in the central nervous system, both in cortical and subcortical areas. It is synthesised from glutamine via glutaminase and released from presynaptic vesicles mainly via voltage-gated Ca2+ channels [Fonnum (1984) in Järventausta et al (2015)]. Glutamic acid decarboxylase transforms glutamate into inhibitory neurotransmitter gamma-aminobutyric acid (GABA), while glutamine synthetase degrades glutamate to glutamine. Glutamate transporter proteins regulate the effects of synaptic glutamate. Extracellular lack of glutamate impairs synaptic plasticity and excess causes oxidative damage and excitotoxicity through excessive accumulation of intracellular calcium [Mark et al (2001) in Järventausta et al (2015)]. Postsynaptically, signals are transmitted by ionotropic receptors: NMDA, alpha-amino-3-hydroxy-5-methyl- 4-isoxazolepropionic acid receptors and kainate receptors and by metabotropic receptors (mGluR1 - mGluR8) [Fonnum (1984) in Järventausta et al (2015)]. Glutamate is involved in cognition and regulation of emotions, as prototypic forms of synaptic plasticity at glutamate synapses are long-term potentiation (LTP) and depression (LTD), in hippocampus, amygdala and prefrontal cortex [Sanacora et al (2012) in Järventausta et al (2015)], and presumably also in the neurobiology of schizophrenia [Coyle et al (2006) in Järventausta et al (2015)]. In addition to glutamatergic effects, ketamine is also involved in several other neurotransmitter systems, like striatal and nucleus accumbens dopamine release, dopamine, serotonin and noradrenaline transporter proteins and GABAergic activity. It has been reported to have neuroplastic effects through activation of trophic factors like nerve growth factor [Robson et al (2012) in Järventausta et al (2015)].

Inhibition of serotonin reuptake is another suggested as a mechanism by which ketamine may confer analgesic effects [Martin et al (1982) in Li & Vlisides(2016)], and ketamine's block of large-conductance KCa channels (BK channels) preferentially suppresses spinal microglia hyperactivation after nerve injury and may explain its potent effects on neuropathic pain [Hayashi et al (2011) in Li & Vlisides (2016)].

Secondary pharmacology

S-ketamine has been found to specifically bind to phencyclidine sites of the NMDA receptors, whereas R-ketamine also binds to sigma sites [Øye et al (1999) in Järventausta et al (2015)]. Both racemic and S-ketamine seem to increase cerebral blood flow (CBF) dose-dependently. Sub-anaesthetic doses of S-ketamine increased the whole brain CBF by 14%,

and anaesthetic doses further extended the effect to 36% [Långsjö et al (2003), Långsjö et al (2005) in Järventausta et al (2015)]. In healthy individuals, S-ketamine increased brain metabolism in several cortical areas and in the thalamus in positron emission tomography, but R-ketamine had the opposite effect in corresponding areas of the brain [Vollenweider et al (1997) in Järventausta et al (2015)]. Furthermore, ketamine also has a slow off-rate (86% trapping) and is an example of a high-trapping antagonist of the NMDA receptor, similar to MK-801 (dizocilpine, nearly 100% trapping). Thus, even after glutamate dissociates from the NMDA receptor, ketamine remains trapped in the closed ion channel and causes continued blockade. Conversely, NMDA receptor antagonists with a fast off-rate (low-trapping), such as memantine, (50–70% trapped) escape the channel before it closes, producing less blockade of physiological NMDA function. This results in fewer side effects (e.g.,sedative or psychotomimetic) and an NMDA antagonist without ‘‘appreciable anaesthetic effects’’ [Sleigh et al., 2014) Li&Vlisides (2016)].

In addition to NMDA-antagonism, S-ketamine acts on a wide-range of other targets, contributing to its unique effects and uses. For instance, ketamine’s relaxant effect on airway smooth muscle has been attributed to its inhibition of L-type voltage-dependent Ca2+ channels [Yamakage et al. (1995) in Li & Vlisides (2016)]. Inhibition of calcium channels may also contribute to observed psychodysleptic effects such as dysphoria, psychosis, altered perception and impaired verbal fluency [Baum & Tecson (1991) Li & Vlisides (2016)]. A block on monoamine transport systems is also thought to contribute to psychotomimetic and sympathomimetic effects [Nishimura et al. (1998) in Li & Vlisides (2016)], and recently, a compelling case has been made that hyperpolarization-activated cyclic nucleotide (HCN) channels —sometimes referred to as neuronal pacemaker channels— significantly contribute to ketamine-induced hypnosis [Chen et al (2009), Zhou C. et al (2013) in Li & Vlisides (2016)]. These channels may mediate the hypnotic effects of volatile anaesthetics as well [Zhou et al (2015) in Li & Vlisides (2016)]. Although ketamine appears to play a role in opioid potentiation [Finck & Nga (1982), Smith et al (1987), Pacheco et al (2014) in Li & Vlisides (2016)], antinociceptive effects mediated by opioid receptors may vary based on receptor subtype [Mikkelsen et al (1999), Pacheco et al (2014) in Li & Vlisides (2016)].

IV.4 Clinical efficacy

Initially, the following indication was claimed:
For the induction and maintenance (with additional injection doses, or by intravenous infusion) of anaesthesia in diagnostic and surgical procedures, as the only anaesthetic or in combination with other anaesthetic agents;

- *Prior to the administration of, or as a complement to, local anaesthesia;*
- *For anaesthesia and pain relief (analgesia) in emergency medicine;*
- *For the treatment of frequent and persistent attacks of dyspnoea (status asthmaticus);*
- *For pain control in mechanical ventilation (intubation),*

Later in the assessment, as already suggested by the RMS in previous rounds, the MAH claimed the following umbrella indication.
"*Esketiv is indicated in children and in adults Esketiv is used for the induction of general anaesthesia and as complement to other anaesthetics.*
Esketiv is a anaesthetic for short-term diagnostic procedures and small surgical procedures which do not require muscle relaxation

For this umbrella indication, which was considered sufficiently justified by literature, the further criteria for a well-established use application (10 years criterion, bridging of the literature data to the current product) were fulfilled. In addition, the use in paediatrics was justified as: the proposed formulation is close to iso-osmotic, has a relatively low pH but it is not buffered thereby allowing fast neutralization after administration. In addition, the drug product does not contain any components that are expected to cause adverse effects in the paediatric population.

To justify the well-established use in new-borns and children, the MAH refers in essence to two articles: Pees (2003) and Green and Krauss (2004).
In the study by Pees the efficacy and side effects of racemic ketamine/midazolam and esketamine/midazolam during cardiac catheterization in 101 new-borns and children (0-11 years) was compared. Ketamine/midazolam and esketamine/midazolam were administered for induction and maintenance of deep analgesia/sedation. It was found that the dosage of esketamine (2.28 mg/kg/h) was lower than that needed for racemic ketamine (3.12 mg/kg/h) ($p = 0.037$) with an analgesic/sedative potency ratio of 1.4:1. More patients were excluded because of ineffective analgesia/sedation or severe side effects in the racemic ketamine group. Pees concludes that S(+)-ketamine proved to be a more efficient analgesic/sedative drug in new-borns and children.
The study by Pees provided support for the use of esketamine for the induction and maintenance of deep analgesia/ anaesthesia in combination with other anaesthetic agents in children (0-11 years).
The Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation in Children by Green and Kraus concerns solely the use of ketamine, and not of esketamine. According to the authors, there is strong support for the use of ketamine in emergency department dissociative sedation for a variety of brief painful or emotionally disturbing procedures, it may also be safely used for longer procedures.

The aim of the study by Vaessen (2017) was to explore if a sedation regimen with low-dose propofol and esketamine performed by trained non-medical sedation practitioners could result in relief of discomfort for the patient and in adequate working conditions for MR-HIFU treatment for uterine fibroids in 20 patients. Mean propofol/esketamine dose was 1309 mg/39.5 mg (range 692–1970 mg/ 23.6–87.9 mg). It was concluded that the combination of propofol and esketamine reduces the discomfort and pain to an acceptable level according to the patients.

The study by Vaessen provided support for the use of esketamine for procedural sedation and analgesia in combination with another anaesthetic agent (propofol).

The study by Adams (1994) uses racemic ketamine or S-ketamine for induction, combined with other analgesics, and as continuous infusion with vecuronium in 40 geriatric patients. The authors concluded that because of the significant improvement in recovery and the reduced quantitative drug load, esketamine offers a clinical advantage compared with racemic ketamine.

The study by Adams (1995) compares esketamine and alfentanil, both in combination with propofol, for maintenance of anaesthesia in 20 geriatric patients. The authors concluded that TIVA with propofol and esketamine had sympathomimetic properties with positive circulatory effects and led to moderate endocrine stimulation. On the other hand, TIVA with propofol and alfentanil showed sympatholytic properties, with negative circulatory effects and a remarkable reduction of endocrine stress response.

Although in a small group of patients, both studies supported the use of esketamine in for the induction and maintenance of anaesthesia in combination with other anaesthetic agents in geriatric patients.

Reference was also made to the online survey by Herzer (2017) that investigated whether clinical practice in the areas of analgosedation and delirium management in patients with intracranial pressure was according to the an Austrian guideline by the Austrian Society of Anaesthesiology, Resuscitation and Intensive Care Medicine. This survey showed that for induction, 33% of the Austrian ICU's use esketamine and beyond 72 h of sedation, 73.3% of intensive care units used esketamine. The article states that "the only aspect that diverges somewhat from the guidelines is the use of remifentanil and esketamine in the early phase up to 72 h." it is however unclear what the place of esketamine in sedation up to 72hours in the guideline is. This article showed the usage of esketamine in induction and maintenance in the Austrian clinical practice in patients with elevated intracranial pressure.

IV.5 Clinical safety

The MAH provided a general overview of common adverse events associated with ketamine use. The general safety profile of (es)ketamine is well known.

The risks for ketamine overdose and dependence are well understood. The risk for an overdose leading to death is low and most likely due to human error. The MAH recommended in the SmPC that esketamine should only be administered by or under supervision of medically qualified anaesthetists or emergency physicians. Equipment to ensure the vital functions should also be readily available. Because esketamine can only be administered within a hospital setting, these precautions are acceptable. It is unclear how widespread ketamine/esketamine abuse is in the EU. However, the MAH has made it clear in the SmPC that caution should be applied with esketamine in patients who have a history of drug abuse.

With the adoption of an umbrella indication, including the justified indications and in line with other esketamine products, no further addition toward the safety profile is necessary.

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 Esketiv.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Anaphylactic reactions - Blood pressure increased - Emergence reactions - Intraocular pressure increased - Laryngospasm - Drug abuse and dependence - Hepatotoxicity
Important potential risks	- Urinary tract-related adverse events, including cystitis
Missing information	- Use in pregnancy and breast feeding

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

Esketiv is considered widely established. For this authorisation, reference is made to clinical studies and experience with esketamine hydrochloride. This active substance has been shown to be effective as an anaesthetic in children and adults. The provided clinical overview is sufficient. No new clinical studies were conducted. This is accepted.

V. USER CONSULTATION

The package leaflet (PL) 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: a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Esketiv 5 mg/ml and 25 mg/ml, solution for injection have a proven chemical-pharmaceutical quality. Esketiv is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

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 Esketiv, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 June 2018.

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