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Public Assessment Report

Name of the Product:

Droperidol Kalceks

1.25 mg/mL and 2.5 mg/mL

solution for injection

(Droperidol)

Procedure number: HU/H/0684/001-002/DC

Marketing authorisation holder: AS Kalceks

Date: 30th April 2021

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the Member States have granted the marketing authorisation of the Droperidol Kalceks 1.25 mg/mL and 2.5 mg/mL solution for injection. The holder of the marketing authorisation is AS Kalceks.

The active substance is droperidol.

Droperidol Kalceks 1.25 mg/mL solution for injection
Each 1 mL ampoule of solution for injection contains 1.25 mg droperidol.

Droperidol Kalceks 2.5 mg/mL solution for injection
Each 1 mL ampoule of solution for injection contains 2.5 mg droperidol.

The other ingredients are tartaric acid, mannitol, sodium hydroxide (for pH adjustment), water for injections.

What Droperidol Kalceks looks like and contents of the pack

Clear, colourless solution, free from visible particles.

1 mL of solution in Type I amber glass ampoules with one point cut. The ampoules are placed in a liner packed in an outer carton.

Pack sizes: 5 or 10 ampoules.

Not all pack sizes may be marketed.

What Droperidol Kalceks is and what it is used for

Droperidol Kalceks is a solution for injection containing the active substance droperidol, which belongs to a group of medicines called butyrophenone derivatives. Droperidol is used to prevent feeling sick (nausea) or vomiting when the patient wakes up after an operation or when the patient receives morphine based painkillers after an operation.

What patients need to know before using Droperidol Kalceks

Droperidol Kalceks must not be given:
- if the patient is allergic to droperidol or any of the other ingredients of this medicine (listed in other ingredients above);
- if the patient is allergic to a group of medicines used to treat psychiatric disorders, called butyrophenones (e.g. haloperidol, triperidol, benperidol, melperone, domperidone);
- if the patient or anyone in his/her family have an abnormal electrocardiogram (ECG) heart tracing;
- if the patient has low levels of potassium or magnesium in his/her blood;

– if the patient has a pulse rate of less than 55 beats per minute (the doctor or nurse will check this), or is taking any medicines that could cause this to happen;
– if the patient has a tumour in his/her adrenal gland (phaeochromocytoma);
– if the patient is in a coma;
– if the patient has Parkinson's disease;
– if the patient has severe depression.

Warnings and precautions

Patients should talk to their doctor, or nurse before this medicine is given to them, as special precautions are necessary:

– if the patient has epilepsy, or a history of epilepsy;
– if the patient has any heart problems or if the patient has any history of heart problems;
– if the patient has a family history of sudden death;
– if the patient has kidney problems (especially if the patient is on long-term dialysis);
– if the patient has lung disease and any breathing difficulties;
– if the patient has prolonged vomiting or diarrhoea;
– if the patient is using insulin;
– if the patient is taking potassium-wasting diuretics i.e. water tablets (e.g. furosemide or bendroflumethiazide);
– if the patient is taking laxatives;
– if the patient is taking glucocorticoids (a type of steroid hormone);
– if the patient or someone else in his/her family has a history of blood clots, as medicines like these have been associated with formation of blood clots;
– if the patient is or have been a heavy drinker (of alcohol).

Other medicines and Droperidol Kalceks

Patients should tell their doctor or nurse if they are taking, have recently taken or might take any other medicines, as a number of medicines cannot be mixed with droperidol.

This medicine **should not be given** if the patient is taking any of the following medicines since the combination increases the risk of irregular heart beat which may lead to heart attack:

What the medicine is used for	**Medicine(s)**
Heart arrhythmia, irregular heart beats	Class IA and III antiarrhythmics
Infection (bacterial)	Antibiotics of the macrolide and fluoroquino-lone type
Malaria	Anti-malaria medicines
Allergies	Antihistamines
Mental illnesses e.g. schizophrenia	Antipsychotics
Heartburn	Cisapride
Parasite infestation or fungal infection	Pentamidine
Nausea (feeling sick) or vomiting	Domperidone
Opioid dependence; pain	Methadone

Metoclopramide and other neuroleptics should be avoided when using this medicine since the risk of movement disorders induced by these medicines is increased.

Other medicines that may affect or be affected when used concomitantly with this medicine.
Droperidol, the active substance in this medicine:
– can increase the effects of sedatives such as barbiturates, benzodiazepines and morphine based products;
– can increase the effects of medicines used to lower high blood pressure;
– can increase the effects of a number of other medicines e.g. certain antifungals, antivirals, and antibiotics.

Patients should talk to their doctor or nurse if they are taking any of these medicines.

Droperidol Kalceks with alcohol

Patients should avoid drinking any alcohol for 24 hours before and after being given this medicine.

Pregnancy, breast-feeding and fertility

If the patient is pregnant, she should inform her doctor who will decide if she should receive this medicine.

The following symptoms may occur in newborn babies, of mothers that have received droperidol in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If her baby develops any of these symptoms she may need to contact her doctor.

If the patient is breast-feeding and will be given this medicine, the treatment will be limited to only one administration. Breast-feeding can be resumed on waking after the operation.

Patients should ask their doctor for advice before taking any medicine.

Driving and using machines

Droperidol has major effect on the ability to drive and use machines.

Patients should not drive or use machinery for at least 24 hours after they have got this medicine.

Droperidol Kalceks contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium free’.

How to use Droperidol Kalceks?

A doctor or nurse will give this medicine to the patients by an injection into a vein.

The dose of Droperidol Kalceks and the way in which it is given will depend on the situation. The doctor will determine how much medicine the patients need based on a number of things including their weight, age and medical condition.

If the patients have any further questions on the use of this medicine, he/she should ask his/her doctor or nurse.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Patients **should tell their doctor or nurse immediately** if they experience any of the following serious side effects:
- Increase in their body temperature, sweating, salivation, muscle stiffness, tremor. These may be signs of so called neuroleptic malignant syndrome (rare side effect)
- Serious allergic reaction or rapid swelling of the face or throat; difficulty swallowing; hives and difficulty breathing (rare side effect)

The following side effects have also been reported:

Common (may affect up to 1 in 10 people)
- Drowsiness
- Low blood pressure

Uncommon (may affect up to 1 in 100 people)
- Anxiety
- Rolling of the eyes
- Fast heartbeat e.g. more than 100 beats per minute
- Dizziness

Rare (may affect up to 1 in 1,000 people)
- Confusion
- Agitation
- Irregular heartbeat
- Rash

Very rare (may affect up to 1 in 10,000 people)
- Blood disorders (usually diseases affecting red blood cells or platelets). The patient's doctor can advise them.
- Change in mood towards sadness, anxiety, depression and irritability
- Involuntary muscle movements
- Convulsions or tremors
- Heart attack (cardiac arrest)
- *Torsade de pointes* (life-threatening irregular heartbeat)
- Prolonged QT interval in electrocardiogram (ECG) (a heart condition affecting the heart-beat)
- Sudden death

Not known (frequency cannot be estimated from the available data)
- Inappropriate anti-diuretic hormone secretion (too much of the hormone is released leading to excess water and low sodium levels in the body)
- Hallucinations
- Epileptic seizures
- Parkinson's disease
- Fainting
- Breathing difficulties

Reporting of side effects

If the patients get any side effects, they should talk to their doctor or pharmacist. This includes any possible side effects not listed in this leaflet. Patients can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects patients can help provide more information on the safety of this medicine.

How to store Droperidol Kalceks?

This medicine should be kept out of the sight and reach of children.

This medicinal product does not require any special temperature storage conditions.

The ampoules should be kept in the outer carton in order to protect from light.

Shelf life after opening the ampoule

The solution should be used immediately after first opening.

Shelf life after dilution

In-use compatibility and stability of Droperidol Kalceks 1.25 mg/mL solution for injection and Droperidol Kalceks 2.5 mg/mL solution for injection with morphine in sodium chloride 9 mg/mL (0.9%) solution for injection was demonstrated in polypropylene (PP) and polycarbonate (PC) syringes for 14 days at 25 °C (protected from light) and at 2 to 8 °C.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

This medicine should not be used after the expiry date which is stated on the outer carton and ampoule after 'EXP'. The expiry date refers to the last day of that month.

For single use only. Any unused solution should be discarded.

The solution should be inspected visually prior to use. This medicine should not be used if there are visible signs of deterioration. Only clear and colourless solutions free from visible particles should be used.

Patients should not throw away any medicines via wastewater or household waste. Their pharmacist should be asked how to throw away medicines they no longer use. These measures will help protect the environment.

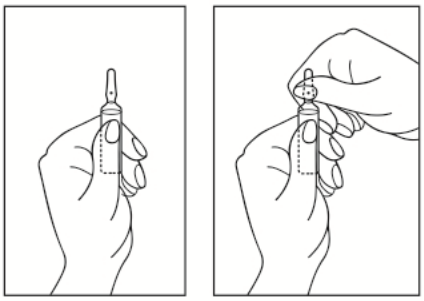
The following information is intended for healthcare professionals only:

Incompatibilities
Incompatible with barbiturates. This medicinal product must not be mixed with other medicinal products except those mentioned in section 'Instructions for use' below.

Instructions for use
For single use only. Any unused solution should be discarded.
The solution should be inspected visually prior to use. Do not use this medicine if you notice visible signs of deterioration. Only clear and colourless solutions free from visible particles should be used.

For use in PCA: Draw droperidol and morphine into a syringe and make up the volume with sodium chloride 9 mg/ml (0.9%) solution for injection.

Instruction of ampoule opening
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Droperidol Kalceks 1.25 mg/mL and 2.5 mg/mL solution for injection. The procedure was finalised at 03/03/2021. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance with the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.
This Decentralised Procedure application (Reference Member State, RMS: Hungary, Concerned Member States, CMS: AT, BE, ES, FR, IT, LV, NL, PT) concerned a generic version of droperidol (Art 10(1) of Dir. 2001/83/EC), under the trade name **Droperidol Kalceks 2.5 mg/mL solution for injection** and a hybrid application conforming to Article 10(3) of Directive 2001/83/EC of the same active substance droperidol under the trade name **Droperidol Kalceks 1.25 mg/mL solution for injection.**
The medicinal product Droperidol Kalceks 2.5 mg/mL solution for injection was developed by AS Kalceks as a generic equivalent to the originator Xomolix 2.5 mg/ml solution for injection.
The marketing authorisation application for Droperidol Kalceks 1.25 mg/mL solution for injection is based on a line extension of 2.5 mg solution for injection, submitted as hybrid application, difference compared to the reference product is in strength (quantitative change in active substance). The reference product was authorised in Austria on 19/12/2007 with only the higher strength, i.e. 2.5 mg/ml.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for **Droperidol Kalceks 1.25 mg/mL solution for injection and 2.5 mg/mL solution for injection.**

The medicinal product is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV) in adults and, as second line, in children (2 to 11 years) and adolescents (12 to 18 years); prevention of nausea and vomiting induced by morphine and derivatives during postoperative patient controlled analgesia (PCA) in adults.

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

The marketing authorisation has been granted pursuant to Article 10(1) and Article 10(3) respectively of Directive 2001/83/EC, therefore the application contained no new clinical or preclinical data, other than supporting literature where necessary.
The Applicant did not perform any bioequivalence studies, as the conditions for a biowaiver, as outlined in the Guideline of the investigation of Bioavailability and Bioequivalence, have been fulfilled.
The reference medicinal product is Xomolix 2.5 mg/ml solution for injection by Chiesi Pharmaceuticals GmBH. The reference product was first authorised on 19/12/2007 in Austria.

II. QUALITY ASPECTS

II.1 Introduction

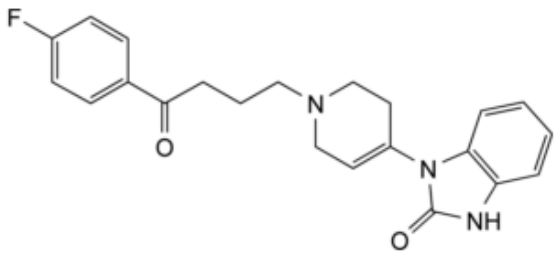
The chemical-pharmaceutical assessment report concerns the application of Droperidol Kalceks 2.5 mg/mL solution for injection via a decentralized procedure according to Article 10(1) of consolidated Directive 2001/83/EC (i.e. a generic application), and of Droperidol Kalceks 1.25 mg/mL solution for injection according to Article 10(3) of consolidated Directive 2001/83/EC (i.e. hybrid application). The products have been developed by AS Kalceks.

The reference medicinal product is Xomolix 2.5 mg/ml solution for injection, which is the product of Chiesi Pharmaceuticals GmbH, Austria.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the Applicant's submission using CEP procedures with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Droperidol
Chemical name: 1-[1-[4-(4-Fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydropyridin-4-yl]-1,3-dihydro-2Hbenzimidazol-2-one
Structure:



The active substance is white or almost white powder. It is practically insoluble in water, freely soluble in dimethylformamide and in methylene chloride, sparingly soluble in ethanol (96 %)
The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.
Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

Re-test period and the packaging materials have been mentioned on the CEP.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the Applicant.

II.3 Medicinal product

The aim was to develop a generic product of Droperidol Kalceks 2.5 mg/mL solution for injection essentially similar to the one which has already been marketed in E.C. Member States for over 10 years. The strength of 1.25 mg/mL was developed in parallel with the generic product. A satisfactory package of data on development pharmaceutics has been presented. The chosen sterilization method of the drug product is justified.
As a result of development studies product with the following appearance was obtained:
- clear colourless solution.

The excipients used in the finished products are tartaric acid, mannitol, sodium hydroxide and water for injections. All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia has been demonstrated by the Applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The primary packaging material of the products is Type I amber glass ampoules. Specification and quality certificate for the packaging are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years is approved with the following special storage restrictions:
‘Keep the ampoules in the outer carton in order to protect from light.’

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of droperidol are well known. As droperidol is a widely used, well-known active substance, no further studies are required and the Applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, droperidol. Overview based on literature review is appropriate.

III.2 Pharmacology

The drug product **Droperidol Kalceks 1.25 mg/mL solution for injection** and **Droperidol Kalceks 2.5 mg/mL solution for injection** contains the active substance droperidol, which is a butyrophenone neuroleptic. Its pharmacologic profile is characterised mainly by dopamine blocking and weak α1 adrenolytic effects. Droperidol is devoid of anticholinergic and antihistaminic activity. Droperidol's inhibitory action on dopaminergic receptors in the chemotrigger zone in the area postrema, gives it a potent antiemetic effect, especially useful for the prevention and treatment of postoperative nausea and vomiting and/or nausea and vomiting induced by opioid analgesics.

At a dose of 0.15 mg/kg, droperidol induces a fall in mean blood pressure, due to a decrease in cardiac output in a first phase, and then subsequently due to a decrease in pre-load. These changes occur independently of any alteration in myocardial contractility or vascular resistance. Droperidol does not affect myocardial contractility or heart rate, therefore has no negative inotropic effect. Its weak α1 adrenergic blockade can cause a modest hypotension and decreased peripheral vascular resistance and may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may also reduce the incidence of epinephrine-induced arrhythmia, but it does not prevent other forms of cardiac arrhythmia.

Droperidol has a specific antiarrhythmic effect at a dose of 0.2 mg/kg by an effect on myocardial contractility (prolongation of the refractory period) and a decrease in blood pressure.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant. The pharmacokinetics of droperidol is well known and extensively described in the product information of the originator and published literature.

Tritium-labeled droperidol, following sc administration to male Wistar rats (0.16 mg/kg), was rapidly taken up by and released from liver and brain. Fifteen minutes after injection, about 60% of the total radioactivity in liver and 35% in blood and in brain was found to originate from metabolites of droperidol. These data indicate that droperidol is very rapidly metabolized. The metabolites disappear from the organs at a slower rate than the parent compound. The brain level of droperidol correlates well with its neuroleptic activity as tested in the antiamphetamine and antiapomerphine test in the rat.

When tritium-labeled droperidol was administered subcutaneously to male Wistar rats (0.16 mg/kg), it was rapidly metabolized and excreted; 30% with urine and 62% with feces. The major part (83%) of the tritium-labeled material was excreted within the first 24 hours. The high total recovery of its radioactivity, 94% in 96 hours, is typical for drugs that are rapidly excreted. Like the majority of neuroleptics of the butyrophenone type, droperidol is metabolized by oxidative N-dealkylation. The major urinary metabolite (a substantial amount is excreted as glycine conjugate) was p-fluorophenylacetic acid, formed in a five-step degradation of beta-(p-fluoropenylacetic acid, formed in a five-step degradation of beta-(p-fluorobenzoyl) propionic acid. Unaltered droperidol is probably excreted with the feces.

III.4 Toxicology

Published information on toxicological studies with droperidol were the basis for the evaluation.
No new toxicity studies were submitted by the Applicant for the product, which is acceptable for these types of applications.

Acute toxicity: The LD50 in mice is reported to be 125 and 250 mg/kg sc, 20 to 40 mg/kg iv, 70 to 90 mg/kg ip, and 195 mg/kg im. Droperidol is atoxic per os. The LD50 in rats is reported to be 640 mg/kg sc, 30 mg/kg iv, 700 mg/kg per os, and 104 to 110 mg/kg im.
The LD50 in dogs is 25 mg/kg iv, in rabbits it is 11 to 12.6 mg/kg iv and 97 mg/kg im; in guinea pigs it is 200 mg/kg im, and in the newborn rat pup the LD50 is 170 mg/kg by intragastric route.
Local toxicity: Droperidol injections into guinea pigs caused necrosis at the site of injection after 24 hours.
Repeated dose toxicity: Rats administered up to 3200 mg/kg droperidol per os over 14 days demonstrated no adverse effects. Rats administered 3 or 12 mg/kg im daily for 30 days demonstrated a dose-related body weight loss and hemorrhaging at the site of injection. Rats given 12, 6 or 2 mg/kg iv daily for 30 days showed a dose-related decrease in body weight of the males. One rat died after 3 doses of 12 mg/kg.
Dogs administered 3 or 12 mg/kg im daily for 30 days showed inflammation at the site of injection. Dogs given 1, 3 or 10 mg/kg iv daily for 30 days showed dose-related sedations and loss of weight. One male dog died of unknown causes after 6 doses of 10 mg/kg. Dogs receiving 10 mg/kg sc developed muscular tremors, ataxia, prostration, and general motor incoordination, with complete recovery within 24 to 48 hours.
Reproduction toxicity, teratogenicity: Rats receiving doses of up to 7.0 mg/kg per os or sc over 3 successive generations showed no adverse effects. Higher doses produced a decrease in the number of pregnancies and body weight loss of pups, an increase in mortality of dams, an increase in number of resorptions, and no change in litter size. Female rats receiving 1.2 and 12 mg/kg iv from the 6th to 18th day of pregnancy showed no adverse effects on reproduction. When droperidol was given to rats during labour, the drug caused an increase in the time of delivery at 3 and 12 mg/kg, but shortened the delivery time at 0.5 and 1.0 mg/kg. Mortality of offspring increased when some dams neglected to remove the placenta from the pups. The percentage of pups weaned was less in the treated groups. There was no effect on litter size or abnormalities.
Mutagenicity/genotoxicity and oncogenic/carcinogenic potential: Mutagenic effects in female rats were observed at high oral doses of 160 mg/kg.

In summary, droperidol is a well-known active substance in human therapy, used since 1961.

Although nonclinical pharmacological, pharmacokinetic and toxicological information is relatively limited on droperidol, these pieces of information, together with its well-documented clinical efficacy and safety profile and provided that its use is restricted to appropriate therapeutic areas in harmony with the Summary of Product Characteristics, makes it recommendable for granting a Marketing Authorisation for Droperidol Kalceks 1.25 mg/mL solution for injection and Droperidol Kalceks 2.5 mg/mL solution for injection.

III.5 Ecotoxicology/environmental risk assessment (ERA)

The Applicant provided an Environmental Risk Assessment (ERA) that is acceptable according to the relevant guidelines (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, EMEA/CHMP/SWP/4447/00 corr 2; Questions and answers on "Guideline on the Environmental Risk Assessment of medicinal products for human use", EMA/CHMP/SWP/44609/2010. Rev.1). It should be noted that the Applicant refers to the draft guideline (EMEA/CHMP/SWP/4447/00 Rev.1., 15 November, 2018), that has not been yet finalised by the EMA.

The submitted calculations are acceptable. The refined PECSw for droperidol in Droperidol Kalceks 1.25 mg/mL solution for injection and Droperidol Kalceks 2.5 mg/mL solution for injection is 0.0004 μg/l is much less than the action limit (0.01 μg/l). So the submitted ERA justifies that the proposed generic medicinal products do not represent a risk for the environment. No further, more detailed risk assessment is required for Droperidol Kalceks 1.25 mg/mL and 2.5 mg/mL solution for injection drug products.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of droperidol are well-known. As Droperidol Kalceks 2.5 mg/mL solution for injection is a generic product, Droperidol Kalceks 1.25 mg/mL solution for injection respectively is an aqueous solution for injection containing the same active substance and excipients as the higher strength, i.e. 2.5 mg/ml, there is no need for further excessive non-clinical studies. The non-clinical part of the application is thus acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

No bioequivalence studies have been performed with the applied product, as the conditions for a biowaiver, as outlined in the Guideline of the investigation of Bioavailability and Bioequivalence, have been fulfilled.
Droperidol Kalceks 2.5 mg/mL solution for injection and Droperidol Kalceks 1.25 mg/mL solution for injection is an aqueous solution containing the same concentration and half quantity of it, respectively, of the active substance as the authorised original product. For detailed assessment of the quality aspects and comparison with the reference product, please see the Quality Aspects.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

The action of a single intravenous dose commences 2-3 minutes following administration. The tranquillising and sedative effects tend to persist for 2 to 4 hours, although alertness may be affected for up to 12 hours.

Distribution
Following intravenous administration, plasma concentrations fall rapidly during the first 15 minutes; this is metabolism independent, redistribution of the drug. Plasma protein binding amounts to 85-90%. The distribution volume is approximately 1.5 L/kg.

Biotransformation
Droperidol is extensively metabolised in the liver, and undergoes oxidation, dealkylation, demethylation and hydroxylation by cytochrome P450 isoenzymes 1A2 and 3A4, and to a lesser extent by 2C19. The metabolites are devoid of neuroleptic activity.

Elimination
Elimination occurs mainly through metabolism; 75% is excreted via the kidneys. Only 1% of the active substance is excreted unchanged with urine, and 11% with faeces. Plasma clearance is 0.8 (0.4-1.8) L/min. The elimination half-life (t½) is 134 ± 13 min.

Pharmacokinetics in special patient groups

Paediatric population
In a study of 12 children (age 3.5 to 12 years), the values for distribution volume and clearance reported were lower than those found in the adult population (0.58 ± 0.29 L/kg and 4.66 ± 2.28 mL/kg × min respectively) and decrease in parallel. The elimination half-life (101.5 ± 26.4 min) was similar to that found in adults.

Bioequivalence

No bioequivalence studies have been performed with the applied product. Droperidol Kalceks 2.5 mg/mL solution for injection and Droperidol Kalceks 1.25 mg/mL solution for injection is an aqueous solution containing the same concentration and half quantity of it, respectively, of the active substance as the authorised original product.
According to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, 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.
The proposed test formulations contain the same active substance and excipients compared to the reference. Components are used in very similar amount - the half quantity for the 1.25 mg/ml strength - as the referred aqueous formulation, except the amount of mannitol which is the same for the two different strengths, nevertheless this is not considered to have significant impact to the active substance's pharmacokinetics.
Since Droperidol Kalceks 1.25 mg/mL solution for injection and Droperidol Kalceks 2.5 mg/mL solution for injection are essentially similar to the reference product Xomolix 2.5 mg/ml solution for injection (Chiesi Pharmaceuticals GmbH, Austria), no bioequivalence study was deemed necessary.

IV.3 Pharmacodynamics

There were no clinical pharmacology studies performed to evaluate the pharmacodynamics of **Droperidol Kalceks 1.25 mg/mL solution for injection and Droperidol Kalceks 2.5 mg/mL solution for injection** and none are required for applications of this type.

Droperidol is a butyrophenone neuroleptic. Its pharmacologic profile is characterised mainly by dopamine blocking and weak α1 adrenolytic effects. Droperidol is devoid of anticholinergic and antihistaminic activity.

Mechanism of action
Droperidol’s inhibitory action on dopaminergic receptors in the chemotrigger zone in the area postrema, gives it a potent antiemetic effect, especially useful for the prevention and treatment of postoperative nausea and vomiting and/or nausea and vomiting induced by opioid analgesics.

Pharmacodynamic effects
At a dose of 0.15 mg/kg, droperidol induces a fall in mean blood pressure, due to a decrease in cardiac output in a first phase, and then subsequently due to a decrease in pre-load. These changes occur independently of any alteration in myocardial contractility or vascular resistance. Droperidol does not affect myocardial contractility or heart rate, therefore has no negative inotropic effect. Its weak α1 adrenergic blockade can cause a modest hypotension and decreased peripheral vascular resistance and may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may also reduce the incidence of epinephrine-induced arrhythmia, but it does not prevent other forms of cardiac arrhythmia.

Droperidol has a specific antiarrhythmic effect at a dose of 0.2 mg/kg by an effect on myocardial contractility (prolongation of the refractory period) and a decrease in blood pressure.

IV.4 Clinical efficacy

No new safety data were submitted and none were required for this application. The Applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of droperidol.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

AS Kalceks has submitted a signed Summary of the Applicant's Pharmacovigilance System (dated on 17/04/2018). AS Kalceks notifies that fulfilling of their pharmacovigilance obligations has contracted a third party service provider - AS Grindeks - for full pharmacovigilance services, including the role of QPPV.

Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the Assessor considers the Summary acceptable.

IV.6.2 Risk Management Plan

The MAH has submitted a risk management plan (version 0.2, final sign off date: 14/10/2020), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to Droperidol Kalceks 1.25 mg/mL solution for injection and Droperidol Kalceks 2.5 mg/mL solution for injection.

Summary of safety concerns	
Important identified risks	• QT Prolongation and Torsades de Pointes (TdP)
Important potential risks	• None
Missing information	• None

The safety concerns are aligned to the most recent version of the RMP of the reference product Xomolix (version 4.0 with DLP of 03/04/2019).

Pharmacovigilance plan

No special important risks have been identified for droperidol, which require additional PhV activities, other than routine PhV, beyond adverse drug reactions reporting and signal detection.

Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to DROPERIDOL KALCEKS' product containing droperidol.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product, **Droperidol Kalceks 2.5 mg/mL solution for injection** and a hybrid application of the same active substance droperidol under the trade name **Droperidol Kalceks 1.25 mg/mL solution for injection.**
Droperidol Kalceks 1.25 mg/mL and 2.5 mg/mL solution for injection is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV) in adults and, as second line, in children (2 to 11 years) and adolescents (12 to 18 years); prevention of nausea and vomiting induced by morphine and derivatives during post-operative patient controlled analgesia (PCA) in adults.

Since Droperidol Kalceks 2.5 mg/mL solution for injection is essentially similar to the reference product Xomolix 2.5 mg/ml solution for injection (Chiesi Pharmaceuticals GmbH, Austria), and the application of Droperidol Kalceks 1.25 mg/mL solution for injection can be accepted as line extension, no bioequivalence study was deemed necessary.
The application contains an adequate review of published clinical data and no bioequivalence study was required.
There were no objections against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The risk/benefit ratio is currently estimated as positive.
The application contains an adequate review of published clinical data.
Approval is recommended from the clinical point of view.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and 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 language used for the purpose of user testing the PIL was Latvian.
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. UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)