Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xomolix 0.5 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution contains 0.5 mg droperidol (1.25 mg/2.5 ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution, free from visible particles.
The pH of Xomolix 0.5 mg/ml solution for injection is 3.0–3.8 and has an osmolarity of approximately 10 milliosmol /kg water.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- 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.

Certain precautions are required when administering droperidol: see sections 4.2, 4.3, and 4.4.

4.2 Posology and method of administration

For intravenous use. Administer slowly (hypotonic solution).

Prevention and treatment of post-operative nausea and vomiting (PONV).
Adults: 0.625 mg to 1.25 mg (1.25 to 2.5 ml).

Elderly (over 65 years): 0.625 mg (1.25 ml).

Renal/hepatic impairment: 0.625 mg (1.25 ml).

Children (2 to 11 years) and adolescents (12 to 18 years): 10 to 50 microgram/kg (up to a maximum of 1.25 mg).

*Children (below the age of 2 years):*not recommended.

For prevention of PONV, antiemetics are indicated in patients at moderate and high risk. The risk should be assessed using standard accepted scales or scores, such as the Modified APFEL Score.

Administration of Xomolix is recommended 30 minutes before the anticipated end of surgery. Repeat doses may be given every 6 hours as required.

In adults, prevention of early vomiting and late nausea may be improved by doses above 0.75 mg, but not greater than 1.25 mg.

In adults and children, higher doses are associated with increased risk of sedation and drowsiness.

Prevention of nausea and vomiting induced by morphine and derivatives during post-operative patient controlled analgesia (PCA).
Adults: 15 to 50 micrograms droperidol per mg of morphine, up to a maximum daily dose of 5 mg droperidol.

Elderly (over 65 years), renal and hepatic impairment: no data in PCA available.

*Children (2 to 11 years) and adolescents (12 to 18 years):*not indicated in PCA.

Continuous pulse oximetry should be performed in patients with suspected risk of ventricular arrhythmia and should continue for 30 minutes following single i.v. administration.

For instructions on dilution of the medicinal product before administration, see section 6.6.

See also sections 4.3, 4.4 and 5.1.

4.3 Contraindications

Xomolix is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Hypersensitivity to butyrophenones;
- Known or suspected prolonged QT interval (QTc of > 450 msec in females and > 440 msec in males). This includes patients with congenitally long QT interval, patients who have a family history of congenital QT prolongation and patients treated concomitantly with medicinal products known to have a risk of *torsades de pointes* through QT prolongation (see section 4.5);
- Hypokalaemia or hypomagnesaemia;
- Bradycardia (< 55 heartbeats per minute);
- Known concomitant treatment leading to bradycardia;
- Phaeochromocytoma;
- Comatose states;
- Parkinson's Disease;
- Severe depression.

4.4 Special warnings and precautions for use

Central Nervous System
Droperidol may enhance CNS depression produced by other CNS-depressant drugs. Any patient subjected to anaesthesia and receiving potent CNS depressant medicinal products or showing symptoms of CNS depression should be monitored closely.

Concomitant use of metoclopramide and other neuroleptics may lead to an increase in extrapyramidal symptoms and should be avoided (see section 4.5).

Use with caution in patients with epilepsy (or a history of epilepsy) and conditions predisposing to epilepsy or convulsions.

Cardiovascular
Mild to moderate hypotension and occasionally (reflex) tachycardia have been observed following the administration of droperidol. This reaction usually subsides spontaneously. However, should hypotension persist, the possibility of hypovolaemia should be considered and appropriate fluid replacement administered.

Patients with, or suspected of having, the following risk factors for cardiac arrhythmia should be carefully evaluated prior to administration of droperidol:
- a history of significant cardiac disease including serious ventricular arrhythmia, second or third degree atrio-ventricular block, sinus node dysfunction, congestive heart failure, ischemic heart disease and left ventricular hypertrophy;
- family history of sudden death;
- renal failure (particularly when on chronic dialysis);
- significant chronic obstructive pulmonary disease and respiratory failure;
- risk factors for electrolyte disturbances, as seen in patients taking laxatives, glucocorticoids, potassium-wasting diuretics, in association with the administration of insulin in acute settings, or in patients with prolonged vomiting and/or diarrhoea.

Patients at risk for cardiac arrhythmia should have serum electrolytes and creatinine levels assessed and the presence of QT prolongation excluded prior to administration of droperidol.

Continuous pulse oximetry should be performed in patients with identified or suspected risk of ventricular arrhythmia and should continue for 30 minutes following single i.v. administration.

General
Caution is necessary when patients are taking medicinal products likely to induce electrolyte imbalance (see section 4.5).

Substances inhibiting the activity of cytochrome P450 iso-enzymes (CYP) CYP1A2, CYP3A4 or both could decrease the rate at which droperidol is metabolised and prolong its pharmacological action. Hence, caution is advised if droperidol is given concomitantly with strong CYP1A2 and CYP3A4 inhibitors (see section 4.5).

Caution is advised when droperidol is used in patients who have, or are suspected of having, a history of alcohol abuse or recent high intakes, as the risk of arrhythmia is increased.

In case of unexplained hyperthermia, it is essential to discontinue treatment, since this sign may be one of the elements of malignant syndrome reported with neuroleptics.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Xomolix and preventive measures undertaken.

The dose should be reduced in the elderly (over 65 years) and those with impaired renal and hepatic function (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interactions

Contraindicated for concomitant use
Medicinal products known to cause *torsades de pointes* through QT prolongation should not be concomitantly administered with droperidol. Examples include:
Class IA antiarrhythmics
- Class III antiarrhythmics
- macrolide antibiotics
- fluoroquinolone antibiotics
- antihistamines
- certain antipsychotic medications
- anti-malaria agents
- cisapride, domperidone, methadone, pentamidine.

Concomitant use of medicinal products that induce extrapyramidal symptoms, e.g. metoclopramide and other neuroleptics, may lead to an increased incidence of these symptoms and should therefore be avoided.

Consumption of alcoholic beverages and medicines should be avoided.

Caution is advised for concomitant use.
Caution is advised when droperidol is used with any other medication known to prolong the QT interval.

To reduce the risk of QT prolongation, caution is necessary when patients are taking medicinal products likely to induce electrolyte imbalance (hypokalaemia and/or hypomagnesaemia) e.g. potassium-wasting diuretics, laxatives and glucocorticoids.

Droperidol may potentiate the action of sedatives (barbiturates, benzodiazepines, morphine derivatives). The same applies to antihypertensive agents, so that orthostatic hypotension may ensue.

Like other sedatives, droperidol may potentiate respiratory depression caused by opioids.

Since droperidolblocks dopamine receptors, it may inhibit the action of dopamine agonists, such as bromocriptine, lisuride, and of L-dopa.

Substances inhibiting the activity of cytochrome P450 iso-enzymes (CYP) CYP1A2, CYP3A4 or both could decrease the rate at which droperidol is metabolised and prolong its pharmacological action. Hence, caution is advised if droperidol is given concomitantly with CYP1A2 inhibitors, CYP3A4 inhibitors or both.

4.6 Fertility, pregnancy and lactation

Pregnancy
A limited amount of clinical data have shown no increase of malformative risk.

Droperidol has not been shown to be teratogenic in rats. Animal studies are insufficient with respect to the effects on pregnancy and embryonal/foetal, parturition and postnatal development.

In newborn babies from mothers under long-term treatment and high doses of neuroleptics, temporary neurological disturbances of extrapyramidal nature have been described. In practice, as a precautionary measure, it is preferable not to administer droperidol during pregnancy. In late pregnancy, if its administration is necessary, monitoring of the newborn's neurological functions is recommended.

Breastfeeding
Neuroleptics of the butyrophenone type are known to be excreted in breast milk; treatment with droperidol should be limited to a single administration. Repeat administration is not recommended.

Fertility
For droperidol, there were no effects on fertility in studies conducted in male and female rats (see section 5.3). The clinical effect of droperidol on fertility has not been established.

4.7 Effects on ability to drive and use machines

Droperidol has major influence on the ability to drive and use machines.
Patients should not drive or operate a machine for 24 hours after droperidol administration.

4.8 Undesirable effects

The most frequently reported events during clinical experience are incidents of drowsiness and sedation. In addition, less frequent reports of hypotension, cardiac arrhythmias, neuroleptic malignant syndrome (NMS) and symptoms associated with NMS, plus movement disorders, such as dyskinesias, plus incidents of anxiety or agitation have occurred.

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1,000 to < 1/100	**Rare** ≥ 1/10,000 to < 1/1,000	**Very Rare** < 1/10,000	**Not known** (cannot be estimated from the available data)
Blood and lymphatic systems disorders				Blood dyscrasias	
Immune system disorders			Anaphylactic reaction; Angioneurotic oedema; Hyper-sensitivity		
Metabolism and nutrition disorders					Inappropriate anti-diuretic hormone secretion
Psychiatric disorders		Anxiety; Restlessness/Akathisia;	Confusional states; Agitation	Dysphoria	Hallucinations
Nervous system	Drowsiness	Dystonia; Oculogyration		Extra-pyramidal disorder;	Epileptic fits; Parkinson's disease;

disorders				Convulsions; Tremor	
Cardiac disorders		Tachycardia; Dizziness	Cardiac arrhythmias, including ventricular arrhythmias	Cardiac arrest; Torsades de pointes; Electrogram QT prolonged	
Vascular disorders	Hypotension				Syncope
Respiratory, thoracic and mediastinal disorders					Broncho-spasm; Laryngospasm
Skin and subcutaneous system disorders			Rash		
General disorders and administration site conditions			Neuroleptic malignant syndrome (NMS)	Sudden death	

Symptoms potentially associated with NMS have occasionally been reported i.e. changes in body temperature, stiffness and fever. An alteration in mental status with confusion or agitation and altered consciousness, have been seen. Autonomic instability may manifest as tachycardia, fluctuating blood pressure, excessive sweating/salivation and tremor. In extreme cases NMS may lead to coma, or renal and/or hepato-biliary problems.

Isolated cases of amenorrhoea, galactorrhoea, gynaecomastia, hyperprolactinaemia, oligomenorrhoea and neonatal drug withdrawal syndrome have been associated with prolonged exposure in psychiatric indications.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic medicinal products - frequency unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the befit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL – Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms
The manifestations of droperidol overdose are an extension of its pharmacologic actions.
Symptoms of accidental overdose are psychic indifference with a transition to sleep, sometimes in association with lowered blood pressure.
At higher doses or in sensitive patients, extrapyramidal disorders may occur (salivation, abnormal movements, sometimes muscle rigidity). Convulsions may occur at toxic doses.
Cases of QT-interval prolongation, ventricular arrhythmias and sudden death have been reported rarely.

Treatment

No specific antidote is known. However, when extrapyramidal reactions occur, an anticholinergic should be administered.
Patients with droperidol overdose should be closely monitored for signs of QT interval prolongation.
Factors which predispose to *torsades de pointes*, e.g. electrolyte disturbances (especially hypokalaemia or hypomagnesaemia) and bradycardia should be taken into consideration.
Pronounced hypotension should be treated by boosting circulation volume and taking other appropriate measures. Clear airways and adequate oxygenation should be maintained; an oropharyngeal airway or endotracheal tube might be indicated.
If required, the patient should be observed carefully for 24 hours or longer; body warmth and adequate fluid intake should be maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Butyrophenone derivatives. ATC code: N05AD08.

Droperidol is a butyrophenone neuroleptic. Its pharmacologic profile is characterised mainly by dopamine-blocking and weak α_1-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 induced by opioid analgesics.

At a dose of 0.15 mg/kg, droperidol induces a fall in mean blood pressure (MBP), 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 α_1-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.

PONV

In a systematic review of 222 studies on prevention of PONV, the risk of PONV was decreased compared to placebo by RR (95% confidence interval) 0.65 (0.60-0.71) for nausea, 0.65 (0.61-0.70) for vomiting and by 0.62 (0.58-0.67) for nausea and vomiting combined.

In a combined analysis of 2061 high risk PONV patients, 1.25mg droperidol was more effective than 4 mg ondansetron or 0.625 mg droperidol in preventing nausea ($p<0.05$; absence of nausea 43%, 29%, 29% respectively), in preventing vomiting (complete response 0-24h 56%, 53%, 48%) and in reducing the need for rescue medication (26%, 34%, 32%).

Monotherapy

A meta-analysis study examined data from 74 clinical trials involving 5351 patients who received 24 different regimens of droperidol and 3372 patients who received placebo or no treatment. The incidence of early (0-6 hours) and late PONV (0-24 hours) in adults and children was analysed (see table).

Early and late outcomes after droperidol compared to placebo or no treatment. Percentages shown refer to incidence of nausea or vomiting.

Parameter		Droperidol Average (range) in %	Placebo/no treatment Average (range) in %
Early outcome (0-6 hours)	Nausea	16 (3-41)	33 (15-80)
	Vomiting	14 (0-56)	29 (6-86)
Late outcome (0-24 hours)	Nausea	45 (1-86)	58 (11–96)
	Vomiting	28 (4-83)	46 (12-97)

Droperidol was more efficacious than placebo or no treatment in preventing PONV in adults and in children.

Combination therapy

A randomised study in 4123 patients assessed the effectiveness of single and combined antiemetic interventions in patients at high risk of PONV. Treatment included 1.25 mg of droperidol or no droperidol; 4 mg of ondansetron or no ondansetron; 4 mg of dexamethasone or no dexamethasone.

The addition of further antiemetics reduced the incidence of PONV, corresponding to an approximate 26% reduction in relative risk of nausea and vomiting for each additional antiemetic. All antiemetics tested were equally effective.

PCA
A systematic review of 14 studies involving 1117 patients receiving PCA was performed.
Droperidol was used in 6 with a dose range of 0.017-0.17 mg/mg of morphine; 0.017-0.33 mg/bolus. The incidence of any emetic event in patients receiving placebo was 66% compared to 30% for patients receiving droperidol.

QTc
In a placebo-controlled study, treatment with droperidol identified a QT interval prolongation at 3-6 min after administration of 0.625 and 1.25 mg droperidol (respectively 15 ± 40 and 22 ± 41 ms), but these changes did not differ significantly from that seen with placebo (12 ± 35 ms). There were no statistically significant differences compared to placebo in the number of patients with greater than 10% QTc prolongation. A second study with 0.75 mg intravenous droperidol and 4 mg ondansetron identified significant QTc interval prolongation (17 ± 9 ms droperidol, 20 ± 13ms ondansetron), with the QTc interval significantly lower after the 90th minute.

A study looking at the combination of ondansetron (4 mg) and droperidol (1 mg) showed that both drugs increased QTc interval separately (17 ± 10 ms ondansetron, 25 ± 8 ms droperidol) but there was no additive effect when given together (28 ± 10 ms).

5.2 Pharmacokinetic properties

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

Metabolism
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 ($t_{½ß}$) is 134 ± 13 min.

Drug Interactions
A study combining ondansetron (4 mg) and droperidol (1 mg) showed that when administered together there was no pharmacokinetic interaction between the two drugs.

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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxic or carcinogenic potential, and reproductive toxicity. A study of oral droperidol in rats showed no impairment of fertility in males or females at up to 20 times the maximum human dose.

Electrophysiological *in vitro* and *in vivo* studies indicate an overall risk of droperidol to prolong the QT interval in humans.

In humans, the free peak plasma concentration is approximately 4-fold higher to 25-fold lower than the droperidol concentrations affecting the endpoints examined in the different *in vitro* and *in vivo* test systems used to assess the impact of this drug on cardiac repolarisation. Plasma levels fall by about one order of magnitude over the first twenty minutes after administration.

Environmental Risk Assessment (ERA)
This product is unlikely to represent a risk to the environment following its prescribed use in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid
Water for injections

6.2 Incompatibilities

Incompatible with barbiturates.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 4 years.
After first opening: For immediate use.

Following dilution: Compatibility of 5 mg droperidol with 100 mg morphine sulphate in 50 ml of 0.9% sodium chloride has been demonstrated in plastic syringes (14 days at room temperature). 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.

6.4 Special precautions for storage

Store in the original package in order to protect from light

For storage conditions after first opening/dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I amber glass ampoules containing 2.5 ml solution for injection, in packs of 10 ampoules.

6.6 Special precautions for disposal and other handling

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

The solution should be inspected visually prior to use. Only clear and colourless solutions free from visible particles should be used.

For use in PCA: Draw Xomolix and morphine into a syringe and make up the volume with 0.9% sodium chloride for injection.

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

7 MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2

2132NP Hoofddorp
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2288/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 September 2011
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10 DATE OF REVISION OF THE TEXT

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