European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR ZUNRISA

International Nonproprietary Name:
casopitant

Procedure No. EMEA/H/C/1040

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AC	Anthracycline/cyclophosphamide
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time-curve
BID	Bis in die (twice daily)
CHMP	Committee on Medicinal Products for Human Use
CINV	Chemotherapy-induced nausea and vomiting
cTnI	Cardiac troponin I
DDI	Drug-drug interaction
Dex	Dexamethasone
ECG	Electrocardiogram
EU RMP	European Union Risk Management Plan
5-HT3	Five hydroxytryptamine (serotonin), subtype 3
FDA	Food and Drug Administration
FLIE	Functional Living Index-Emesis
GCP	Good clinical practice
GEE	Generalised Estimating Equations
GSK	GlaxoSmithKline
h	hour(s)
HEC	Highly emetogenic chemotherapy
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
ITT	Intent-to-treat
IP	Intraperitoneal
IV	Intravenous
L	Liter
MEC	Moderately emetogenic chemotherapy
mg	milligram
MITT	Modified Intent-to-treat
mL	millilitre
NK-1	Neurokinin subtype-1
NRS	Numerical Rating Scale
OD	Once-daily
Ond	Ondansetron
PDCO	Paediatric Committee
PDNV	Post-Discharge Nausea and Vomiting
PET	Positron Emission Tomography
PIP	Paediatric Investigational Plan
PO	Per os (oral route of administration)
PONV	Post-operative nausea and vomiting
PET	Positron emission tomography
QTc	QT interval corrected for rate
QTcF	Corrected QT interval for heart rate (Fridericia's)
SA	Scientific Advice
SAE	Serious adverse event
SD	Single dose
SmPC	Summary of Product Characteristics
SP	Substance P
tmax	Time to maximum concentration
ULN	Upper limit of normal
VAS	Visual Analogue Scale

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Zunrisa 50 & 150 mg tablets, in combination with other anti-emetic medications, indicated for the prevention of:

- Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC).
- Nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC).
- Postoperative nausea and vomiting (PONV)

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

II. EXECUTIVE SUMMARY

Casopitant, is a piperidine derivative that is used as its mesylate salt in the submitted application. It concerns the first MAA for casopitant in the EU and is considered as a new chemical entity.

Casopitant is an orally bioavailable, selective NK-1 (neurokinin subtype 1) receptor antagonist. It has been developed for the treatment of depression and anxiety but has also anti-emetic activity. The presented application concerns the prevention of emesis due to chemotherapy (CINV) or surgery (PONV). The first agent approved in the class was aprepitant (Emend). It is used for similar indications.

Casopitant mesylate is proposed as film-coated tablets (50 and 150 mg). It should be noted that the Applicant has withdrawn the 'Powder and solvent for solution for infusion' (90 mg) formulation.

For CINV indication, a one-day treatment (150 mg single tablet) is proposed. For PONV indication, the recommended dose is a single tablet of 50 mg.
It should be noted that the Applicant has withdrawn the originally requested 3-day CINV IV/oral dose regimen and the IV dose form.

No major clinical safety issues remain as only the one day casopitant regimen has been retained. The administration of strong CYP 3A4 inhibitors is not recommended in patients treated with casopitant. Significant QTc prolongation has been observed in a clinical study when casopitant was associated with ketoconazole. In the analysis of casopitant's clinical cardiac safety profile, there were some more peripheral oedema in the casopitant group. However, an incidence of peripheral oedema as high as 4% is associated with the treatment regimen with doxorubicin and cyclophosphamide in patients treated for metastatic breast cancer. The other terms more specific for heart failure were balanced between casopitant and non-casopitant groups.

The applicant has resolved the majority of the PK issues. The following follow-up measures (FUM) will be provided in 2009-2010:
- Drug-drug interaction study NKV103444 between casopitant and cyclophosphamide.
- PK and safety study NKT102783 of multiple oral doses of casopitant in subjects with renal impairment.

The CHMP awaits some minor PK modifications of section 4.5 of the SmPC.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The drug substance, *i.e.* Casopitant, is a piperidine derivative, used in the current application as the mesylate salt. The submitted dossier concerns the first MAA for casopitant in the EU and is considered as a new chemical entity.
The molecule possesses three asymmetric carbon atoms, resulting in 8 potential stereoisomers. Only one isomer (1R, 2R, 4S) is defined as the drug substance, the other ones are appropriately controlled by the quality of the starting materials and intermediates, by the used synthesis scheme and by analytical control methods.
The manufacture part is satisfactorily described and only some questions on clarification are asked, mostly for the submission of original reports that are not included in the dossier. By day 150, the majority of these issues have been solved and only one point for clarification remains. The development is thoroughly worked out, using the "Quality by Design Approach", in which the "Design Space" and "Proven Acceptable Ranges" were defined.
The elucidation of the structure of the drug substance is adequately discussed. An overview of all potential impurities and those that are really observed is given, although the data proving their structure is missing and is asked for. By day 150, only an issue on specifications for methansulfonate impurities remains.
The control of the drug substance is acceptable, provided some questions on further clarification would be addressed appropriately.
The re-test period has been determined 36 months using the storage condition "Store up to 30°C". The latter one is questioned. An acceptable justification was given by day 150.

Drug Product

Casopitant mesylate is proposed as film-coated tablets (50 and 150 mg) and as powder and solvent for solution for infusion (90 mg). The injectable form is withdrawn from the application after day 120.
For CINV indication, a one day treatment (150 mg single tablet) or a three-days treatment (first day 90 mg intravenously, second and third day 50 mg oral treatment). The three-days dosing regimen is also withdrawn from the application after day 120.

For PONV indication, the recommended dose is a single tablet of 50 mg.

Film-coated tablets (50 and 150 mg)

Casopitant film-coated tablets, 50 mg, are pale orange, hexagonal, biconvex tablets, with one side plain and one side debossed with an identifying code GSK 72. The tablets contain 50 mg of casopitant free base as casopitant mesylate.
Casopitant film-coated tablets, 150 mg, for oral administration, are white, hexagonal, biconvex tablets with one side plain and one side debossed with an identifying code GSK 77. The tablets contain 150 mg of casopitant free base as casopitant mesylate.
Both tablets are packed into aluminium-aluminium blisters.

The pharmaceutical development has been thoroughly performed partly within a framework of *Quality by design*. For the first three manufacturing unit operations, *i.e.* granulation, blending and compressing, "Proven Acceptable Ranges" on parameters were defined. A separate genotoxic risk assessment is included as well. This development section supports the manufacturing process that has been validated on full-scale batches.

The drug products are controlled by appropriate quality attributes using validated analytical procedures. All quality attributes and their acceptance limits are justified appropriately. For assay and related substances, the analytical methods were also validated using the "Quality by design" principle for which "Proven Acceptable Ranges" are defined using appropriate statistical techniques.
The stability study supports the proposed shelf-life (36 months for 50 mg and 36 months for 150 mg) without any special storage condition.

For the film-coated tablets and 'powder and solvent for solution for infusion', only some minor clarifications are asked. These are all cleared out by day 150 for the film-coated tablets.

Powder and solvent for solution for infusion
The injectable form is withdrawn from the application after day 120.

III.2 Non clinical aspects

Pharmacology

In accordance with the *Guideline on non-clinical and clinical development of medical productrs for the prevention of nausea and vomiting associated with cancer chemotherapy (CPMP/EWP/4937/03)* the Applicant has characterised the *in vitro* affinity of the compound with the human target receptor cloned in CHO cells. Also the activity of the corresponding animal NK-1 receptor from species used in the non-clinical programme was studied. As such, brain homogenates from mouse, gerbil, marmoset, and ferret were investigated. However, there are no data on the affinity of casopitant for the NK-1 receptor of rat and dog. The structure of NK-1 receptors is highly conserved between species. Nevertheless, NK-1 receptors can be segregated into two groups: on one hand human, guinea pig, hamster, gerbil, cow, marmoset, ferret and rabbit and on the other hand rat, mouse and chicken. There are no data that allow for a classification of the dog NK-1 receptors. Species-related variation in the primary sequence of the NK-1 receptor severely influences the potency of non-peptide antagonists in different species. Clustering of various species related to heterogeneity in amino acid sequence of trasnmembrane segments 1-7 exactly matches clustering of species-related differences in the affinities of non-peptidic tachykinin NK-1 receptor antagonists. The experimental data provided demonstrate that affinity of casopitant for the NK-1 receptor between the two identified clusters of species differs by a factor of 10.

The nonclinical data presented in this submission have also demonstrated that casopitant antagonizes NK-1 agonist-induced intracellular calcium mobilization *in vitro*.
In addition, at D121 the Applicant submitted a complimentary study where the ability of casopitant to inhibit SP induced increases in [^{3}H]-IP accumulation following pre-labelling of the cells with [^{3}H]-myo-inositol was measured. SP produced a concentration-dependent increase in [^{3}H]-IP accumulation in human NK-1-HEK293 cells with a pEC_{50} of 8.56 ± 0.08. Casopitant produced a concentration-related decrease in the maximal response produced by SP, consistent again with non-surmountable antagonism. The apparent pK_B for casopitant was 9.05 ± 0.09, versus SP. It could be concluded that casopitant is a potent non-surmountable antagonist at the human cloned NK_1 receptor.

The high potency, good brain penetration and long receptor occupancy of casopitant was demonstrated in the gerbil foot tapping model, and brain penetration was confirmed in PET ligand studies in monkeys. Brain penetration has also been confirmed in human PET studies [Report VM2004/00019/01].
At D121 the Applicant submitted a complementary study to investigate the correlation between the ability of casopitant to reverse NK-1 receptor agonist GR73632-induced foot tapping behaviour and NK-1 receptor occupancy in the brain. Oral administration of 0.1 and 0.3 mg/kg casopitant reverses foot tapping behaviour induced in male gerbils by the NK1 receptor agonist GR73632. Receptor occupancy in the dorsal striatum was dose-related and correlated with the pharmacodynamic responses with >90% occupancy required for maximum activity. These data demonstrate that casopitant is a potent centrally acting NK_1 receptor antagonist in vivo.

In accordance with the *Guideline on non-clinical and clinical development of medicinal products for the prevention of nausea and vomiting associated with cancer chemotherapy (CPMP/EWP/4937/03)* the Applicant has characterised the anti-emetic properties of casopitant in the ferret model of cisplatin-induced emesis.
In the acute cisplatin-induced emesis model, a single IP dose of casopitant dose-dependently inhibited both retching and vomiting with an ID_{50} of 0.08 mg/kg. (ID_{CR} = 2 mg/kg). In the delayed cisplatin-induced emesis model, a single dose or 3 daily IP doses of casopitant resulted in anti-emetic activity with ID_{50}s of 1.3 and 0.28 mg/kg, respectively (IDCR = 11 and 6 mg/kg for single and daily dosing, respectively). Rescue from established emesis following casopitant administration was demonstrated

in both the acute and delayed cisplatin-induced emesis models with an ED50 of 0.08 mg/kg in both models.
With respect to the indication PONV no specific primary pharmacodynamic studies have been conducted. The ferret cisplatin-induced nausea and vomiting model is accepted to be predictable for determination of potential CINV activity in humans. However, its usefulness in the prediction of efficaciousness in preventing PONV had not been justified by the Applicant. The Applicant was requested at Day 120 to discuss about the relevance and implications of not having induced emesis in the ferret models with other emetogenic agents, such as morphine, loperamide, ipecac syrup, cooper sulphate or apomorphine and not only with cisplatin (chemotherapeuthic agent), to support the PONV indication. In the Responses Document after D120 LoQ, the Applicant has provided a new study where anti-emetic properties of casopitant were tested against non-chemotherapy-related emetogens to support PONV indication. Casopitant treated ferrets (1 mg/kg (i.p.)) showed complete anti-emetic response against morphine (1.0 mg/kg, s.c), loperamide (0.5 mg/kg, s.c.), copper sulphate (12.5 mg/kg, p.o.) and ipecac (1 mL/kg, p.o.) (1 out of 4 non-complete responder). Moreover, casopitant decreased peri-emetic events (nausea) in morphine, loperamide and ipecac treated animals. Casopitant inhibited morphine-induced emesis in a dose related manner (ID_{50} of 0.028 mg/kg; ID_{CR} of 0.22 mg/kg vs. ID_{CR} of 2 mg/kg (i.p.) in the acute cisplatin-induced emesis model in the ferret). From a non-clinical point of view, new data submitted by the Applicant demonstrated casopitant anti-emetic activity against non-chemotherapy-related emetogens in the ferret and can be considered sufficient to support PONV indication.

Furthermore, the mechanism of action of the 5-HT3 and NK-1 receptor antagonists, ondansetron and casopitant, have been shown to be complementary and can result in synergistic anti-emetic effects at sub-optimal doses of the two agents.

A number of human metabolites, including the major metabolite of casopitiant, M13, which exists as a mix of two diastereoisomers, are also potent and selective antagonists of the human NK-1 receptor. However, as animal studies demonstrated reduced brain penetration of the metabolites in comparison to that of casopitant, their role in the pharmacological action of casopitant is unclear. Nevertheless, considering that exposure to M13 in plasma is similar to that of casopitant, it has the potential in nonclinical species to contribute to the overall pharmacological activity.

Casopitant and the active metabolites M13,M31 and M12 were capable of weakly inhibiting the L-type calcium channel and the T-type calcium channel in the micromolar range. Activity at these receptors is thought to contribute to the dystocia, cardiovascular, hemodynamic and gingival effects observed in safety pharmacology and toxicology studies at high doses. It is considered that there is a low risk of these effects occurring in humans as they were only seen following much higher doses, and consequent exposures in the nonclinical studies.
Human plasma exposure at the maximum proposed oral and IV therapeutic doses amounts to 716 and 1630 ng/ml. At the highest Cmax value (worst case scenario) and taking into account an unbound fraction in human of 0.4%, exposures of 9.12 nM of casopitant are reached. High exposure margins make that clinically relevant interactions with receptors other than the NK-1 receptors are unlikely.

Several summaries of in vivo studies not related to the claimed indication were submitted in this application: depressive disorders, insomnia and overactive bladder. Anxiolytic effect and some effects on micturition were observed following a single administration of casopitant 1 mg/kg (p.o. and i.d. administration, respectively). Single doses up to 3 mg/kg (i.v. and p.o.) were needed to observe effects on insomnia and further effects on micturition.

These doses are in the same range as those at which complete responses of the prophylactic anti-emetic activity in the PD in vivo studies were observed. Therefore it should be considered that these secondary effects might be observed during casopitant treatment for anti-emetic purposes. However, due to the short duration of the treatment, the relevance of these effects is expected to be minor.

The package of safety pharmacology studies provided comprises the safety pharmacology core battery required by *ICH Guideline on Safety pharmacology studies for human pharmaceuticals (S7A*). All safety pharmacology core battery studies were performed in compliance to GLP principles.

A receptor binding assay was provided. Clinical signs indicative of activity on the CNS have been reported at high doses of casopitant (200 mg/kg). These effects were expected considering that casopitant exerts its anti-emetic activity at the CNS level, and brain penetration had been already demonstrated, as well as the long duration of the effects due to the long lasting occupancy of the receptors. The NOAEL for neurobehavioral effects in the rat following oral administration was determined to be 60 mg/kg. Exposure at this dose provides an acceptable safety margin (rat exposure at 60 mg/kg (p.o.) 8.1-fold higher than the human exposure at the oral therapeutic dose (150 mg)). The NOAEL for convulsions in repeat toxicology studies was determined to be 200 mg/kg (rat).
Casopitant effects on respiratory system were quantified and evaluated in rats up to 200 mg/kg. Only at this dose, a statistically significant decrease in respiratory rate, accompanied by increases in inspiration and expiration times was observed. The NOAEL was determined to be 60 mg/kg. It does not seem to be any cause of concern related to casopitant effects on respiratory function.
In vitro studies in isolated dog Purkinje fibers, and in hERG channels showed that casopitant decreases action potential duration at 50% and 70% of repolarisation, and that it is able to inhibit hERG channel tail current in a concentration-dependent manner. However, concentrations at which these effects are observed are high enough compared to human exposures, that none of these effects would be expected in humans at therapeutic doses. In dog telemetry studies, decreases in both QT and QTc interval duration were observed at high doses of casopitant (200 mg/kg) administered orally or intravenously. The NOAEL following oral and intravenous administration were 10 mg/kg and 15 mg/kg, respectively. The exposures at these doses provide a sufficient safety margin compared to human exposure (around 3-fold).
At D120, the Applicant was requested to elaborate on the risk for undue interaction between casopitant and 5HT3 receptor antagonist and cytostatic drugs on cardiac electrophysiology. The substances could target different ion channels and the combined effect is not known. In their response, the Applicant referred to clinical data regarding the potential for QT prolongation of casopitant alone and in combination with ketoconazole (worst case scenario in clinical practice). These data show that the administration of casopitant alone is not followed by significant QTc prolongation. However, when a strong CYP 3A4 inhibitor is associated with casopitant, significant QTc prolongation can occur. Therefore the administration of strong CYP 3A4 inhibitors is not recommended in patients who have been treated with casopitant. Relevant statements are included in the SPC (sections 4.3 and 4.4).
Additionally, assessment of ECG results for both CINV and PONV Phase III studies where casopitant was given with cytotoxic drugs such as doxorubicin as well as 5HT3 antagonists indicate that QTc is not prolonged with casopitant administration in this setting.
And finally, clinical pharmacokinetic interactions studies conducted with ondansetron, dolasetron, and granisetron (NKV100787 and NKV110483), demonstrated no pharmacokinetic interaction of clinical relevance was observed, and no ECG abnormalities were noted using standard cardiac monitoring.
Consequently, the clinical data obviate the need for further non-clinical investigations.

There were no data on the possible interaction of casopitant with dexamethasone. However, it is to be anticipated that both drugs will be co-administered in the clinical setting for CINV. In addition, concomitant administration of casopitant with drugs used for PONV had not been considered (e.g. droperidol, haloperidol, tropisetron, palonosetron and transdermal scopolamine). One in vitro study on pharmacodynamic drug interactions has been provided. Casopitant was tested in combination with cisplatin (10 μM), docetaxel (0.5 μM) and doxorubicin (1.0 μM) on 4 human breast tumor cell lines (BT-474, MCF-7, MDA-MB-468 and MX-1). No antagonism neither synergism was found in the combination data. However, it should be considered that several of the combinations pairs lacked sufficient activity for complete analysis due to the lack of single agent anti-proliferative activity of casopitant in the cell lines tested.

In addition, due to the lack of in vivo studies, and considering casopitant is always going to be administered concomitantly with other anti-emetic medication and chemotherapeutic agents or anaesthesia, data provided from the only in vitro study are considered rather limited.

Chemotherapeutic agents selected could be considered adequate to represent highly and moderately emetogenic chemotherapy, as regarded in the claimed indication, as cisplatin is considered emetogenic level 4 (high emetogenic risk, >90%), docetaxel, emetogenic level 2 (low risk, 10-30%), and

doxorubicin emetogenic level 3 (moderate risk, 31-90%) according to Hesketh, 2008. However, at Day 120 the Applicant was requested to further discuss:
a. the sufficiency of the number and type of chemotherapeutic agents and cell lines tested.
b. the potential interactions with other anti-emetic (i.e. 5-HT3 antagonists), chemotherapeutic and anaesthetic agents that will/could be co-administered with casopitant for the claimed indications (CINV and PONV).
In the Responses Document after D120 LoQ,
a. the Applicant has provided justification on the selection of the number and type of chemotherapeutic agents and cell lines tested. The selection criteria for the representative combinations tested: to cover a range of low to highly emetogenic chemotherapy, to cover chemotherapies used in pivotal Phase II and III clinical trials, and to assess the potential for pharmacokinetic drug-drug interactions (casopitant CYP3A4 inhibitor combined with docetaxel, a CYP3A4 substrate), are considered adequate. The selection of breast cancer cell lines is also considered adequate given doxorubicin and docetaxel are approved for use in breast cancer and are known effective antiproliferative agents against breast cancer cell lines. The lack of in vivo studies in murine xenograft models can be considered acceptable.
b. In a new study submitted (Report UH2009/00006/00), suboptimal doses of palonosetron co-administered with casopitant showed synergistic anti-emetic activity in cisplatin-induced emesis model in ferrets, as previously observed for ondansetron (Report UH2007/00066/00 submitted in the original MAA).

In a second new study submitted (Report UH2009/00003/00), the antiemetic potency of casopitant in ferret MEC model when co-administered with cyclophosphamide (80 mg/kg) and doxorubicin (6 mg/kg, i.p.) was ID_{50} of 0.032 mg/kg (vs. ID_{50} of 0.08 mg/kg in the cisplatin-induced acute emesis model, and ID_{50} of 1.3 mg/kg in the cisplatin-induced delayed emesis model). Casopitant inhibited the total number of nausea behaviours with an ID_{50} of 0.246 mg/kg in the MEC model (vs. ID_{50} of 0.01 and 0.37 mg/kg in the cisplatin-induced delayed emesis model). Therefore, it is supported the Applicant's view that these data suggest casopitant has potent antiemetic activity in the MEC model in ferrets, although the effects on nausea behaviours are not as marked as seen in the HEC model of emesis using cisplatin (HEC data from Reports UR2004/00002/00 and UR2004/00002/00, submitted in the original MAA).

In these two studies, as well as in previously submitted reports, no indication of adverse pharmacodynamic interaction on co-administration of casopitant with either $5\text{-}HT_3$ antagonists (ondansetron, palonosetron), or HEC/MEC agents (cisplatin/ cyclophosphamide, doxorubicin) has been noted.

Potential interactions with dexamethasone, and some different chemotherapeutic agents (vinorelbine, paclitaxel, etoposide, paclitaxel and docetaxel) have been addressed clinically.

Although no specific non-clinical drug-drug interaction studies were performed with anaesthetic agents, more than 2000 patients receiving a variety of anaesthetic agents in the PONV setting were exposed to casopitant during Phase II and Phase III trials.

These two issues should be further addressed from a clinical point of view.

Pharmacokinetics

A comprehensive package of nonclinical pharmacokinetic, distribution, metabolism and excretion studies was conducted with casopitant in mouse, rat and dog, the species used for toxicity evaluation of casopitant, and in human.

Following oral administration of casopitant, absorption was relatively rapid in all preclinical species as for humans.
Across the nonclinical species, casopitant has a moderate half-life and its volume of distribution is greater than total body water indicating substantial association with tissues.

Elimination of DRM from animal tissues was slow. *In vitro* protein binding of casopitant ranged from high in rat to very high in dog and human, with low association with blood cells.
Limited data indicate that the presence of casopitant and M13, M12 and M31 is responsible for the eye reddening observed in the 39-week repeat dose toxicity study in the dog. Recovery is observed which parallels the disappearance of casopitant and the 3 metabolites in tear film samples collected after 24 weeks.
The observed preferential distribution and accumulation of parent and/or in rats and dogs, most probably contributes to the corresponding target organ toxicity in the various repeat dose toxicity studies. Taking into account the intended short term clinical use (CINV and PONV) where treatment will maximally extend to 6 cycles, long-term accumulation of casopitant and/or metabolites is not considered of clinical significance.

All metabolite profiling studies demonstrated that casopitant was extensively metabolised in both nonclinical species and in humans. The principal components observed in human plasma after administration of casopitant were unchanged casopitant, M13 and M12. Together with those metabolites, oxygenated derivatives of depiperazine open piperidine ring acid were also observed.

Plasma metabolic profiles after single oral and IV administration of casopitant to humans were qualitatively similar. Qualitatively similar metabolites were also observed following single and multiple oral dosing of casopitant to male human volunteers.

Preliminary data on two ongoing metabolite profiling studies in plasma and myocardium (rat and dog), and skeletal muscle samples (dogs) were submitted, where previously unidentified metabolites were seen. At D121, the Applicant submitted the final study reports.
The submitted data demonstrate that following a single and a repeat oral administration of casopitant to female rats the principal radiolabelled components in plasma, other than the unchanged casopitant; were M13 after single dose and M206 after repeat dose. Other notable components included M31, M3/M166 and M12. A similar metabolic pattern was observed also in myocardium samples with few other notable metabolites including the major M76, M134, M200 and M206.
Following a repeat oral administration of casopitant to male Beagle dogs for 14 days the principal radiolabelled components in plasma were casopitant, M13 and M12. Other notable components included M31, M134 and M169. This cluster was also found in myocardium, skeletal muscle, kidney and lung homogenate extracts with M134 likely as the major radiometabolite; M76, M13 and M203 were found as notable. All metabolites detected in tissues were found also circulating, with the exception of M203, not detected in plasma.
Following 20 days of recovery from the last dosing, a number of metabolites were still detectable: in myocardium, M31, M134, M200 and M203 were observed. Those metabolites together with M169 and M76 were also present at much higher concentrations in tissues than in plasma, following 14 days of treatment.

At D121 the Applicant has submitted a new *in vivo* metabolite profiling study where the six major metabolites of casopitant were identified and quantified in beagle dog's plasma and myocardium. Unchanged casopitant, the M13, M12, M31, M76, M134 and M200 were all detected and quantified in dog myocardium following repeat oral dosing of casopitant 40 mg/kg/day for up to 26 weeks. M200 and M134 were the major metabolites in dog myocardium with levels increasing over the time and still quantifiable after 22 weeks recovery following 13 weeks of treatment. No correlation was identifiable between myocardium and plasma levels for casopitant or any metabolites.

The major route of elimination was via the faeces, which accounted for approximately 90% (mouse and rat), 80% (dog) of the dose. Negligible amounts (2 to 7% of the dose) are excreted in the urine in all species tested. These data were confirmed in a definitive study submitted by the Applicant at Day 121. Elimination in mice following a single oral dose of casopitant was largely by metabolism via the faeces (86% of the administered dose), with the predominant route of metabolism being oxidation of the parent molecule. The principal metabolite in faecal exctracts was the oxidised derivative M50. Urinary excretion was a minor route of elimination (6% of administered dose, with cleavage (N-dealkylation) and oxidation of the molecule being the predominant route of metabolism (metabolites M28 and M135 accounting for ~ 27% of the urinary radioactivity each). The recovery of radioactivity

was nearly complete in all species. Approximately 100% recovery of radioactivity was achieved by 168 hours (7 days) post dose in rats and mice, while approximately 90% of the radioactivity was recovered by 216 hours (9 days) post dose in dogs

Qualitatively, all of the relevant metabolites of casopitant observed in humans were detected with a similar if not higher exposure in the nonclinical species.
All casopitant relevant metabolites which have been identified in human plasma are also present at similar or higher exposure level in the animal species used for the repeat dose toxicity studies at NOAEL. As such no separate metabolite toxicity studies are required.

In vitro data suggest that the human cytochrome P450 (CYP) enzyme mainly involved in casopitant metabolism is CYP3A4. In vitro and in vivo studies have indicated that there is the potential for clinical drug-drug interactions between casopitant and CYP3A4, CYP2C8, P-glycoprotein and OATP1B1 substrates.
These pharmacokinetic and metabolic disposition studies have shown that the animal species used during its toxicological evaluation were appropriate for the assessment of the safety of casopitant for human use.

Toxicology

Single dose toxicity studies with casopitant were performed in mice, rats and dogs. Only studies in rats were GLP compliant.

Most evident toxicity signs were related to exaggerated CNS activity. Those findings were not unexpected considering casopitant is a potent centrally active NK-1 receptor antagonist, which also has high brain penetration and relatively long duration of receptor occupancy. Rats administered i.v. bolus of casopitant at 100 mg/kg, presented red discolouration of the urine revealing severe hemolysis. Gastric findings in the intravenous administration study in rats seemed to be consistent with those found in repeated toxicity studies.
The oral MNLD of casopitant in rats was defined as 1000 mg/kg. The intravenous MNLD in rats was 50 mg/kg.

Exacerbated central effects of casopitant at high doses and exposures were common across species tested.
However, it could be considered that a sufficient safety margin exists (between 6 and 16 for rat, and between 7 and 13 for dog)[1]. Exposures (C_{max}) in rats at which effects were observed, were at least 19-fold the human C_{max} at the maximum oral dose of 15 mg/kg, and 8-fold the human C_{max} at the proposed intravenous dose (90 mg/kg). In dogs, these differences in exposure were even higher. In addition it is reported than no clinically significant incidences of convulsions or seizures have been reported in the clinical evaluations in humans.

Gastric mucosal changes have been observed in the rat repeat dose oral and intravenous studies, and in the pivotal repeat dose oral studies in the dog. These effects include chief cell/reduction/atrophy, changes in gastric pit, isthmus and neck mucous cell hypertrophy/hyperplasia. These effects were completely recovered in rats after 15 weeks off-dose (in the 26-week oral study), and in dogs after 24 weeks off-dose (in the 39-week oral study). In a specific mechanistic study to compare the effects of oral versus intravenous administration, incidence and severity of the findings were increased following oral administration. Contribution of local action of casopitant was demonstrated (presence of NK-1 receptors in chief cells in the stomach). Progression to gastric metaplasia would not be expected, based on the appearance of the mucosa, and no changes in neuroendocrine cells.
Pepsinogen levels were measured in cryopreserved serum samples obtained from female CD rats exposed for 4 days to up to 600 mg/kg/day of casopitant. Although increased, no dose-dependent increase in pepsinogen in serum is observed. Moreover, these data obtained at very high dose levels and short exposure time do not allow to draw conclusions regarding pepsinogen levels at the lower dose levels at which stomach toxicity was observed in both rat and dog.

[1] Daily safety margin based on animal terminal mean AUC at no-effect level vs. human AUC at 90 mg IV (6240 ng.h/mL).

In addition, contradictory findings (decreased mucosal pepsinogen levels) were reported in the 4-week mechanistic study in male SD rats administered casopitant PO at 200 mg/kg/day (VD2004/00017/00). Although the non-clinical safety studies indicate very low safety margins for casopitant-induced stomach changes, clinical studies of up to 12 weeks duration (doses of 80 – 120 mg/day) did not show a clear trend for changes in serum pepsinogen I and II levels and very few gastric adverse events were attributed to casopitant treatment. In addition, non-clinically observed stomach changes were seen to be fully reversible following recovery in both the 26-week rat and the 39-week dog repeat dose toxicity studies.

Phospholipidosis was commonly observed in casopitant non-clinical toxicity studies at multiple sites which often included liver, lungs, lymphoid tissues and sometimes heart. This phenomenon of accumulation of intracellular phospholipids with lamellar bodies due to an impaired phospholipid metabolism of the lysosome is a known effect of a variety of drugs including cationic amphiphilic drugs (CADs). Casopitant and some of its metabolites are CADs. Recovery was not complete, although in progress after 15 weeks (rat) or 24 weeks (dog) of dosing withdrawal. Toxicological consequences of phospholipidosis are not well known yet (Anderson N, 2006). However, monitoring measures (presence of phospholipidotic lamellar bodies in peripheral blood cells) were included in the clinical development of the compound, after 4 weeks of daily oral treatment up to 120 mg/day, revealing no increases in lymphocytes with lamellar bodies in human subjects.

Cardiac changes have been seen in long term studies in animals. In rats, myocardial degeneration/fibrosis and increases in heart weight were recorded at 150 and 200 mg/kg (26-week oral study), accompanied by increases in plasma levels of Troponin I and CK. Ultrastructural changes seemed to be due to phospholipidosis. No histological or biochemical effects were observed in rats up to 13 weeks of oral treatment and 14 days of i.v. treatment although increased heart weights were noted in all oral studies. Similar effects were observed in dogs in the 39-week oral study from 10 mg/kg casopitant. Reversibility was not complete in either of these long term studies. It was estimated by the applicant that the total ingested drug burden at the no-effect level in the 26-week oral study in rats and in the 39-week oral study in dogs were 94-fold and 59-fold the total quantity administered in a 6 cycles clinical regime. Cardiac TnI was measured in clinical studies up to 12 weeks duration with daily doses up to 120 mg/day, and no changes attributable to treatment with casopitant have been observed.
A specific study was performed to investigate the effects of casopitant on the presence, onset, progression and potential reversibility of cardiovascular changes in Beagle dogs treated with a cardiotoxic dose (40 mg/kg/day) for up to 26 weeks.
Sustained (24 h) decreases in systolic and diastolic blood pressure, and increases in heart rate were observed during the study, but fully reverted after a 4-week recovery period. Increases in PR interval and a decrease in QTc interval were noted, and only partially reverted at the end of the recovery period. A persistent increase of the Left Ventricular mass was evident from Day 63 in treated animals. However, there was no evidence of functional impairment. Serum markers of cardiac hypertrophy and cardiomyocyte injury, NT-pro-BNP and cTnI respectively, were increased during the study duration, and still elevated at the end of the recovery period.
These cardiotoxic effects of casopitant, some of them not fully reverted, have been reported to be related to casopitant and DRM retention/accumulation with phospholipidotic-like features, and probably to alterations in calcium physiology. However, considering the estimated cumulative systemic exposure to casopitant at the no-effect level in dog (10 mg/kg/day for 39 weeks) and rats (60 mg/kg/day for 26 weeks) is around 65-fold and 100-fold, respectively the cumulative human exposure over 6 cycles of casopitant treatment, short-term and cyclic use of casopitant for PONV and CINV is not expected to impose a cardiac risk on patients.
At D121 the Applicant has submitted a new investigative study to characterise the onset and progression of cardiac changes expected at casopitant dose of 40 mg/kg/day (p.o.) when administered for 6, 13, 20 or 26 weeks, and recovery from any changes following a treatment-free period of 22 weeks after 13 weeks of treatment.
In-life cardiac changes were initially noted over the first 6 weeks of treatment (i.e. increase in NT-pro BNP from Week 2; increases in cTnI, aldosterone and CKMB and decreases in K^+ levels from Week 6) progressing with treatment and associated with the appearance of increased heart weight and QTc interval by Week 6, and associated ultrastructural changes in the heart (i.e. intracytoplasmic

multilamellar bodies in the sarcoplasm of myofibres and blood vessel endothelial or smooth muscle cells) progressing in severity with duration of dosing, but with adverse findings at light microscopy appearing (i.e. minimal to moderate myofibre degeneration/necrosis) only after 20 weeks of treatment. Although signs of reversibility were apparent, full recovery did not occur after a 22 week treatment-free period.
Cardiotoxicity findings appeared earlier than in previous repeat dose toxicity studies and specific investigative study submitted in the original MAA. Exposure data from this study and the relative safety margins for the reported findings should be provided/further addressed by the Applicant to enable a complete assessment and discard potential cardiotoxic risk for humans at the claimed indications (PONV and CINV).
An investigative study on the potential mitochondrial effects of casopitant or its metabolites in heart tissue samples collected from the 26 week repeat dose study in male beagle dogs was submitted at D121. Inhibition of Ca^{2+} -induced mitochondrial swelling was observed in mitochondria isolated from the heart of dogs following oral administration of casopitant (40 mg/kg/day) during 26 weeks, with interim kills. This finding may reflect alterations in mitochondrial Ca^{2+} fluxes and could be one of the factors contributing to the cardiotoxicity observed in dogs with casopitant. It should be considered that in previous secondary pharmacodynamic studies, casopitant and some of its metabolites (M12, M13 and M31) showed L- type calcium channel activity, and that those metabolites have been seen to accumulate in myocardium.

An additional specific toxicity study was performed to evaluate the influence of the co-administration of casopitant and doxorubicin in the known cardiotoxic effect of the last one. At a doxorubicin dose of 0.8 mg/kg, observed effects were similar when administered alone or with casopitant 60 mg/kg. At a doxorubicin dose of 1.25 mg/kg, a marked systemic toxicity was observed, and a trend to increased cardiotoxicity when administering casopitant with doxorubicin. Therefore, potential doxorubicin cardiotoxicity enhancement cannot be discarded in humans.
An *in vitro* investigative study on the potential of casopitant (mesylate salt) and three of its principal or active human circulating metabolites, M12, M31 and M13 for cytotoxicity, phosphorylation, mitochondrial toxicity and oxidative stress was undertaken in the cultured human myeloid cell line U937, and submitted at D121. Obtained results suggest that at non-cytotoxic concentrations, the tested drug molecules have a limited potential to cause disruption to mitochondrial function and redox homeostasis. The phospholipidosis data (Nile Red and EM) suggests that the metabolite M31 in comparison to the other compounds under study has a greater potential for causing phospholipidosis in vivo at equivalent dose levels. However, it should be considered that metabolites tested in this study are not the major metabolites determined in dog myocardium (M200 and M134; Report VD2008/00352/00), still quantifiable after 22 weeks recovery following 13 weeks of treatment, and therefore the ones more likely related to the observed cardiotoxicity.

Swollen gums were observed in the dog 39-week repeat dose oral study among animals treated with at least 25 mg/kg. This effect led to treatment discontinuation in the Week 30 for the high dose group. After 24 weeks of cessation of treatment, effects were only completely reverted in females, and just partially in males. The applicant has provided justification regarding some calcium blockers being able to produce these gingival changes. Gingival hyperplasia is widely described in literature for some calcium blockers as nifedipine or amlodipine, as well as for other drugs such as cyclosporine A or phenytoin. Casopitant showed some binding affinity and functional activity in calcium channel L-type and T-type receptors during the pharmacodynamic development program, so it seems feasible to be a secondary pharmacologic effect.
It did not seem to represent a risk for humans since it has not been noted in any of the other non-clinical studies, and the estimated safety margin from this dog study is at least 76-fold based on cumulative exposure over 6 cycles of casopitant treatment. It has neither been reported in humans up to 12 weeks studies at a dose of 120 mg/day. However it should be considered to be included in the RMP as a potential risk, especially considering it is not always reversible after discontinuation of treatment and might require surgical intervention.

Renal findings were observed in rat, dog and mouse after oral administration of casopitant at high doses (150 mg/kg/day in rat, and ≥ 25 mg/kg/day in dogs) from Week 4 onwards. These pathological changes included multifocal tubular degeneration and necrosis around the arcuate arteries, bilateral

nephropathy, tubular dilatation and fibrosis/cysts in the kidney. They were associated with altered kidney functional parameters such as elevated urea and urinary protein output, increased water consumption, urine output and variable plasma phosphorus and potassium values. Casopitant exposures (AUC) at the no-effect level were 9.2-fold (mouse), 16.3-fold (rat) and 3.8-fold (dog) the human exposure at the i.v. dose of 90 mg, and consequently no risk for humans is expected at the proposed regimen for the prevention of PONV and CINV.

Thyroid follicular cell hypertrophy and centrilobular hepatocyte hypertrophy were observed in the rat 4, 13 and 26-week repeat dose toxicity studies at doses ≥ 15 mg/kg/day. Also some variations in clinical chemistry and haematological parameters were observed. These changes can be attributed to hepatic microsomal enzymes induction and/or phospholipid accumulation. Thyroid follicular cell hypertrophy is secondary to induction of T4-UDP-glucuronyl transferase (well known phenomenon in rats; McClain, 1989). However, there does not seem to be a cause of concern in humans since it is reported that rat thyroid gland is inherently more active than human one, and thyroid hormone homeostasis is more readily disrupted in rats compared to humans.

Other reported findings were: reddening of the eyes, and darkening of organs and tissues at autopsy. This last finding was not associated with any histopathological or functional changes; it could be related to retention or accumulation of drug and/or DRM. It is not expected to impose a risk on humans given the indicated short term treatment.

Reddening of the eyes was observed in dog studies of ≥ 4 weeks duration. Ocular irritancy studies showed casopitant to be a moderate to severe ocular irritant. At Week 30 of the 39 daily repeat dose oral toxicity study, casopitant DRM was detected in tear fluid, but not at the end of the recovery period. Ocular findings were moreover fully reverted. Therefore, casopitant can be considered not to pose a risk to humans under the proposed dosing regimen, as there was no reported evidence of ocular findings or reports of irritations in patients treated with casopitant during the clinical development program.

Considering: no-effect level has been identified in all species tested for most of the findings reported above, the sufficient exposure safety margin (nonclinical species vs. human), given the proposed limited duration and cyclic use of casopitant, as well as that no effect or no clinically relevant changes have been seen in the multiple dose studies in humans for all the findings reported above, these findings are not expected to impose a clinical risk on patients in the proposed indications in this MAA.

A dog 52-week repeat dose oral study was still in progress at the time of submission of this MAA. Preliminary findings submitted do no differ to those previously observed up to 39-weeks dosing. The definitive report was submitted in the Responses Document after D120 LoQ. In this study, casopitant exposure increased more than dose proportionally although no differences were noted between sexes, and systemic exposure was generally stable along the study. No evidence of supraproportionality was noted in previous studies at these dose levels. This effect could be due to accumulation of casopitant and DRM after a prolonged dosing period (52-weeks).
Aggressive behaviour of males at all doses during the first 9 weeks could be related to casopitant treatment.
Most reported findings confirmed those observed in the previous study in beagle dogs up to 39 weeks: reversible reddening of the sclera, excessive ear wax, non-completely reversible foamy/pigmented macrophages in the lymphoid tissues and lungs (at 25 or 40 mg/kg/day in the 39-week study, and at 10 mg/kg/day in the 52-week study) and reversible myofibre degeneration in skeletal musculature (at 40 mg/kg/day in the 39-week study, and at 3 or 10 mg/kg/day in the 52-week study). It can be concluded that similar findings were observed in this second study despite casopitant doses were lower, due to the longer duration of the dosing period.
Increases in alkaline phosphatase were also noted in the study up to 39 weeks, although in that case ALP levels returned to baseline during the recovery period, while in the study up to 52 weeks these increases were maintained to the end of the recovery period.
The most relevant finding was the increased level of cardiac Troponin I (up to 29X pre-treatment values) in the 10 mg/kg/day dose group, accompanied in two female dogs by myocardial degeneration/inflammation. At the end of the 13-week recovery period no microscopic findings were

observed, although one animal continued to show increased cardiac Troponin I values. Non complete recovery in cTnI values had already been noted in the 39-week study. Cardiotoxicity due to casopitant and DRM would be further discussed in line with new submitted studies at D121.
The overall assessment of repeat dose toxicity studies has not been affected by the submitted final report of the 52-week repeat dose oral toxicity study in dogs. All the findings confirmed those previously observed up to 39-weeks. The NOAEL for casopitant cardiotoxicity was 3 mg/kg/day, lower than in the 39-week study (10 mg/kg/day). The cumulative systemic exposure to casopitant at the no-effect level in dog (3 mg/kg/day for 52 weeks) is 19-fold the cumulative human exposure over 6 cycles of casopitant treatment.

All definitive genotoxicity studies (*in vitro* Ames and human lymphocyte assays and an *in vivo* chromosome aberration assay) utilised casopitant mesylate salt, and were conducted in full compliance with GLP.
Casopitant did not show any mutagenic or clastogenic potential when assessed using in vitro tests of gene mutations in bacteria, primary DNA damage and chromosomal aberrations studies in-vitro and in-vivo.

Carcinogenicity studies (up to 2 years duration) were not finalised at the time of submitting this MAA. The applicant argues they would not be needed to support the short-term use of casopitant in CINV and PONV, based on ICH Guideline S1A (Guideline on the need for carcinogenicity studies of pharmaceuticals).
However, as studies were currently ongoing, the final report was required to be filed when available to completely discard the carcinogenic potential of casopitant. In the Response Document after D120 LoQ the Applicant said that the reports of these carcinogenicity studies will be filed after the review of the MAA is completed. However, it should be highlighted that these final reports should be submitted as soon as available (foreseen March 2009), to adequately complete this assessment.
Non-definitive data from the carcinogenicity studies revealed two cases of benign squamous cell papilloma in the uterus of rats dosed 100 mg/kg/day casopitant, and three cases of squamous cell carcinoma in the mid- and high dose groups (40 and 100 mg/kg/day) in the rat study. These effects are considered a rodent specific response, since the rodent endocrine effector organs tend to be more susceptible to disturbance of hormonal regulation. However, as reported in Appendix 1A, this could be due to direct action of casopitant (NK-1 receptor antagonist) at the hypothalamic level, controlling prolactin and LH release. In particular, prolactin inhibition in rats leads to luteolysis with consequent reduced progesterone production and therefore oestrogen dominance. Increased incidence of benign endometrial polyps observed in the uterus of mice females (40 and 75 mg/kg/day casopitant) have been also attributed to a possible oestrogen dominance, although the incidence is within the normal background ranges reported by the laboratory where the study was conducted for mice of that age.
Further assessment of carcinogenicity-related findings will be made when definitive study reports will be available.

Casopitant did not show any toxic effect on mating, fertility and gonadal function in male Sprague Dawley rats; neither on mating, fertility, early embryonic and embryofetal development in female Sprague Dawley rats.
The only observed effects in males were increased salivation at all doses and decreased body weight gains and food consumption at 150 mg/kg/day in week 1, and decreased body weight gain at 60 mg/kg/day in week 5. In females, body weight loss at ≥ 30 mg/kg/day pre-cohabitation, decreased body weight gain at 30 mg/kg/day between Days 0 to 10 pc, and decreased food consumption at 100 mg/kg/day pre-cohabitation and Days 0 to 6 pc were observed.
Increased salivation was a common effect in repeat toxicity studies that could be related with poor palatability of the test article. Decreases in food consumption and losses in body weight could also be related to test article taste. As no other finding has been noted it is not considered to be relevant for humans.
Based on the results of the dose range toxicity study in rabbits (poor tolerability and low systemic exposure), this species was not considered to be suitable for further reprotoxicity studies. Therefore, as embryotoxicity testing in two mammalian species is required by CPMP/ICH/386/95 Note for Guidance on the detection of toxicity to reproduction for medicinal products and toxicity to male fertility (ICH5SA), mice and rat were the species chosen. This two rodent species selection was

considered acceptable by the Spanish Agency during the pre-submission meeting held on 21 may 2008.
Placental transfer was demonstrated in mice and rats and suckling pups from treated female rats.
Principal findings in embryofoetal development toxicity studies were the increased incidence of cleft palates, cervical ribs and incompletely ossified phalanges of the hindpaw observed at 300 mg/kg/day (p.o.) in mice. As supported by literature submitted by the applicant, teratogenic effects such as cleft palate and delayed skeletal ossification have been observed in mice associated with high corticosterone levels. An investigative study was performed to see the effects caused by casopitant on corticosteroids in vivo. Casopitant-related time-dependent increases in ACTH and plasma corticosterone levels have been observed. No toxicokinetic data were gathered in this study. However, taking into account plasma exposures obtained in a 5-day mouse toxicokinetic study, a safety margin of about 2-fold as compared to human AUC following oral administration of 150 mg casopitant, is obtained. The SPC clearly states that Casopitant is not recommended during pregnancy (section 4.6) and findings and exposure margins are taken up in section 5.3.
In the absence of adrenal changes in the repeat dose toxicity studies, more specifically in the 13-week mouse repeat dose toxicity study, ACTH and corticosterone levels have not been monitored. Histopathology has indeed demonstrated very limited effects on the adrenals of female mice (e.g. subcapsular hyperplasia). Taking into account that casopitant is indicated for short term use (single dose) in CINV (multiple cycles) and PONV and taking into account that casopitant is not recommended to be used during pregnancy, no further non-clinical studies or clinical monitoring of cortisol and ACTH are deemed necessary.
Casopitant at 100 mg/kg/day showed high toxicity in F0 dams and F1 litters. Three F0 females were found dead, and necropsy examinations revealed thick yellow content within the heart, enlarged spleens, livers and lymph nodes, and dark red discoloration of the lungs. In addition, F0 dams presented red vaginal discharge, hair loss, and increased salivation. At this dose level, it was observed a decrease in F1 pups survival, pups born, live litter size and post-natal survival between birth and postnatal day 4. One of the major findings was evident dystocia in F0 females, possibly related to inhibition of the uterine activity through casopitant calcium channel blockade. Dystocia was not observed at lower casopitant doses, neither in F1 dams (30 mg/kg/day means a casopitant exposure 4.2 times the maximum human exposure after an i.v. dose of 90 mg). Considering this finding, casopitant should not be used in pregnant women, especially close to parturition.
Reduction in body weight gain and food consumption was observed in F0 and F1 at 100 mg/kg, and in F0 at 30 mg/kg casopitant. F1 litters (F0 dams administered 100 mg/kg/day) showed affected auditory startle responsiveness. F1 neonatal developmental and neurobehavioral toxicity NOAEL was 30 mg/kg/day.
No study in juvenile animals has been provided. It can be acceptable as current claimed indication for casopitant is only for the prevention of CINV and PONV in adult patients.

The ocular, skin and local lymph node, and *in vivo* dog studies were performed in full compliance with GLP regulations. However, the pivotal in vitro hemolysis study was performed just in accordance with the general principles of the GLP regulations.

Dermal and ocular irritancy, and skin sensitisation potential studies, were performed to assess worker health and safety hazards associated with manufacture of the drug product. Casopitant was considered to be a mild to moderate skin irritant and a mild to severe ocular irritant (mild to moderate in vitro; severe ex-vivo). Casopitant was considered to be a non-sensitizer under the conditions of the mouse local lymph node assay performed.

In the 14 day i.v. studies in rat and dog, the veins into which casopitant was infused displayed evidence of irritation (mural necrosis and inflammation) and minor effects reflecting the haemolytic potential of casopitant in rats, including decreased erythroid parameters, increased platelet counts and lymphoid activation. Results of specific haemolytic studies in vitro showed that casopitant concentration intended for human use (0.36 mg/mL) was not haemolytic at infusion rates of 3.3, 8.3 or 10 mL/min. Local irritancy and hemolysis were observed at 3- and 6- fold higher concentrations. Some discomfort attributed to erroneous administration was observed in one dog in the intravenous irritancy in vivo study.

Casopitant showed to be a non-sensitizer under the conditions of the mouse local lymph node assay.

Some parameters were evaluated in standard repeat toxicity studies for signs of immunotoxicity (CPMP/SWP/1042/99 Note for guidance on repeated dose toxicity). Some of the most commonly observed related findings were: increased circulating neutrophils and lymphocytes, increased spleen weight, thyme hypertrophy and thymic involution. In addition, adrenal cortical congestion and increased adrenal weight accompanied by decreased body weight and physical activity could be attributed to stress-related immunotoxicity at high casopitant doses (not well tolerated), as reflected in *CHMP/167235/2004 Note for guidance on immunotoxicity studies for human pharmaceuticals (ICH S8)*. It has to be considered that neither increased incidence of infections nor increased occurrence of tumours have been reported in the standard toxicity studies.
Considering the majority of the patient population for whom the drug is intended is immunocompromised, in this case by concomitant treatment with chemotherapy in cancer patients, additional immunotoxicity studies were warranted.
A specific study was performed to investigate the effects of casopitant (mesylate salt) on the primary antibody response to T-cell dependent antigen, keyhole limpet hemocyanin (KLH). The only immunotoxic effect observed was a decrease in anti-KLH IgG, but not IgM in females at 100 mg/kg/day. However, considering it was noted at exposures higher than 4.2 (male) and 6-fold (female) the human exposure at 90 mg i.v., it can be supported the applicant's view that immune suppression associated with administration of casopitant in humans will not be expected.

Taking into account the recommendations in the Guideline on the non-clinical investigation of the dependence potential of medicinal products (EMEA/CHMP/SWP/94227/2004), the Applicant has conducted 2 behavioural studies to assess dependence potential of casopitant, namely a study investigating reinforcing properties and a drug discrimination study. In the secondary pharmacological studies no clinically relevant affinities for known targets involved in drug dependence have been identified, although it should be acknowledged that no functional assays have been carried out and that the affinity for the cannabinoid receptors has not been investigated. No study has been performed to investigate withdrawal syndrome. Taking into account the absence of non-clinical signs of withdrawal symptoms (clinical signs, body weight, food consumption) during the recovery period in both the 26-week rat (15-week recovery) and the 39-week dog (24-week recovery) repeat dose toxicity studies, the absence of clinical reports of withdrawal or rebound effects from studies of up to 12-weeks duration and the fact that casopitant is indicated for short term use (single doses) in CINV (multiple cycles) and PONV, no further non-clinical studies are deemed necessary.
Reinforcing properties: Human plasma exposure at the maximum proposed IV therapeutic doses amounts to 1630 ng/ml. Since a similar level of self-administration to that of vehicle is observed for casopitant at mean plasma levels of 3892 ng/mL, which corresponds to 2.4-fold the maximum human exposure following a IV dose of 90 mg, it is concluded that casopitant exhibits negligible reinforcing properties.
Drug discrimination: Plasma levels of casopitant following oral administration of 10 mg/kg were 189ng/ml at 180 minutes post-dose. Human plasma exposure at the maximum proposed oral dose amounts to 716 ng/ml. Taking into account that a maximum dose of 18 mg/kg of casopitant is administered to the animals during the study the dose levels used in this drug discrimination study are considered to entail plasma concentrations that are lower than those attained in the clinical setting. Consequently this study is not considered relevant for predicting human effects. Taking into account the absence of clinically relevant affinities for known targets involved in drug dependence, the absence of reinforcing properties in baboons at plasma exposure levels corresponding to 2.4-fold the maximum human exposure following an IV dose of 90 mg, the fact that casopitant is indicated for short term use (single doses) in CINV (multiple cycles) and PONV and animal welfare considerations, supplementary drug discrimination studies in baboons at clinically relevant doses of casopitant are not deemed necessary.

The metabolic pathways in humans are also found in pre-clinical species, especially in female rats, and male and female dogs. As the exposures of the most relevant human metabolites M13, M12, and M31 in mouse, rat and dog are similar to those in humans, the toxicology profile of these metabolites can be considered to be sufficiently investigated as part of the parent casopitant development program.

According to CHMP Guidelines CHMP/ICH/2738/99 Note for guidance on impurities in new drug products, and CHMP/ICH/2737/99 Note for guidance on impurities testing: impurities in new drug substances, process impurities, and degradation products, at/over the qualification threshold, were qualified.
The proposed specified impurities and degradation products can be considered to have been appropriately qualified.
However, considering casopitant salt intended for human use is the mesylate salt, and taking into account the potential formation of related impurities during the production process (e.g: ethyl methanesulfonate, methyl methanesulfonate), the applicant was asked at Day 120 to justify in case they were produced, if there would be any potential genotoxic/carcinogenic risk. Assuming the genotoxic potential of methyl methanesulfonate, ethyl methanesulfonate and isopropyl methanesulfonate, the Applicant has been required to establish a routine control in drug substance to ensure levels below the TTC for the maximum daily dose of 150 mg/kg casopitant. This point is not resolved yet from a Quality point of view. This issue could be resolved once the appropriate controls would be in place to assure non-concern levels.

Considering the pharmacopoeial grade and wide use of all excipients used in the formulation of casopitant tablets and casopitant injection, no further environmental assessment on these ingredients is required. Also components of packaging of casopitant tablets and casopitant injection comply with relevant regulation and are introduced into the environment from a wide variety of sources. Therefore it is supported no further environmental assessment of packaging material is required.

Casopitant has been thoroughly investigated for its potential environmental risk. However, the Applicant has provided a recalculation of the PEC based upon Fpen refinements and this separately for the indication CINV and PONV. The proposed Fpen refinements are not based on published epidemiological data and are not in line with the recommendations as stated in the Guideline on the environmental risk assessment of medicinal products for human use (cfr. CPMP/SWP/4447/00). Consequently these are not acceptable.
In the initial MAA, a phase I and phase II assessment have been submitted based upon the calculated Phase 1 PEC of 0.75 µg/L.

III.3 Clinical aspects

Pharmacokinetics

The applicant has resolved the majority of the PK issues. Some modifications should still be done in section 4.5 of the SmPC and the following follow-up measures (FUM) should be provided in 2009-2010:

- Drug-drug interaction study NKV103444 between casopitant and cyclophosphamide (mid 2010)
- PK and safety study NKT102783 of multiple oral doses of casopitant in subjects casopitant with renal impairment. The clinical study is completed and the clinical pharmacology study report is being prepared (2009).

Given the elimination properties of casopitant (<8% of the dose is excreted in the urineas, casopitant or metabolites), it was unlikely that mild or moderate renal insufficiency will significantly impact the safety or pharmacokinetics of casopitant or metabolites. The SmPC recommends however casopitant should be used with caution in subjects with severe renal impairment. The PK and safety study NKT102783 of multiple oral doses of casopitant in subjects with renal impairment is now completed and demonstrates, after age-adjustment, that mild or moderate renal impairment had no relevant impact on casopitant or M13 (total or unbound) exposure following single- or repeat dose administration.

The applicant should however clarify the number of patients included in the study NKT102783 (renal impairment) in each group since there is a mention of n=6 per group and it is mentioned in the assessment of the Applicant‘s responses that only 2 patients with mild and 1 with moderate renal

impairment are included. The statistical relevance of these small sample sizes should also be discussed. The CHMP suggests not to modify the proposed wording on renal impairment until the MAH responds to the question raised on the statistically relevance of these small sample sizes.
No clinical significant differences in casopitant PK were observed in subjects with mild or moderate hepatic impairment. Since further data are not available in patients with severe hepatic impairment, the use of casopitant should be contraindicated in patients with severe hepatic impairment.

Gender is not a significant covariate and males and females exhibit similar casopitant exposures.

Taking into account the revised single dose administration, the increased exposure observed in Day 3 in Japanese males is not clinically relevant. The casopitant and M13 exposures observed in male Japanese subjects after 150 mg single dose oral administration were similar to those observed in Western populations at this dose.

Concerning the potential involvement of CYP3A5 in the metabolism of casopitant and the genotype frequencies of CYP3A5 in different ethnic groups, the applicant mentions that the involvement of CYP3A5 in the metabolism of casopitant has not been assessed. CYP3A5 is very probably involved in the metabolism of casopitant in humans. However, as mentioned by the applicant, there are very few specific substrates for CYP3A5 and coexpression with CYP3A4 (which is also highly variable) makes clinical interpretation and conclusions regarding these polymorphisms difficult.

The safety and efficacy of casopitant in patients less than 18 years has not been established.

No clinically significant differences in casopitant PK were observed in elderly subjects. However, since there is limited data in very elderly subjects (≥75 years), the EU Risk Management Plan (RMP) includes on-going standard and additional pharmacovigilance practices to monitor for, and minimise, any potential risk.

The drug-drug interactions of casopitant are well discussed in the SmPC:

The SmPC mentions correctly that concomitant administration of casopitant with strong inducers of CYP3A is not recommended as this is likely to result in significantly reduced plasma concentrations and decreased efficacy of casopitant.

The casopitant SmPC in section 4.5 is now completed with the statement that caution should be used during co-administration of casopitant with strong inhibitors of CYP3A. The CHMP does not judge a contraindication necessary.

As for other compounds, casopitant is at the same time CYP3A inhibitor and also CYP3A inducer as suggested in the oral contraceptive study. However, inhibition of CYP3A predominates clearly over any induction effect and the posology has been modified for a single dose administration. Special warning is present in section 4.4 of the SmPC mentioning that casopitant dose regimens may reduce the efficacy of hormonal contraceptives. The patients should use alternative methods of contraception when casopitant is administered.

The docetaxel interaction study has now been completed and no interaction between casopitant and docetaxel is demonstrated.

For the cyclophosphamide study (NKV103444), due to problems of GCP-non compliance, the applicant is continuing to enrol subjects so that at least sixteen evaluable subjects complete the study and therefore no statistical analyses of PK data can be provided until now. Study NKV103444 will be provided as a follow-up measure (FUM) mid 2010.

The applicant has provided a table for the estimation of the interaction potential of oral casopitant and CYP3E substrates takes into account the main anti-cancer drugs not studied and gives a good opinion of the magnitude of interactions, midazolam serving as an upper limit of any potential interaction.

Additional drug-drug interaction studies are not judged necessary as the potential interaction is sufficiently predicted for each anti-cancer drug.

The results of the Study NKV110483 assessing the PK interaction between repeat doses of oral Casopitant and repeat Oral Doses of Dolasetron, Granisetron or Rosiglitazone are confirmed by the new study described in the article from Adam LM et al.: "Effect of casopitant, a novel NK-1 antagonist, on the pharmacokinetics of dolasetron and granisetron", GSK, USA. Support Care Cancer, from February 2009. The conclusions are that none of the changes (in exposure) observed are considered clinically meaningful and coadministration of casopitant with dolasetron or granisetron was well tolerated.

Pharmacodynamics

Casopitant belongs to a new class of antiemetics that involve substance P as a potential therapeutic target. Substance P, a regulatory peptide of the tachykinin family, mediates a number of biologic effects by binding to a specific neuroreceptor, neurokinin 1 (NK-1). Substance P is released from the gut as part of the emetic response. The antiemetic effect of NK-1 receptor antagonists is, therefore, believed to be predominantly centrally mediated, by suppressing the activity of the nucleus tractus solitarius, the site where vagal afferents from the gastrointestinal tract converge with inputs from the area postrema and other regions of the brain believed to be important in the control and integration of emesis.

Clinical efficacy

CINV

Casopitant, a novel agent of a new class known as the NK-1 receptor antagonists, meets the persistent clinical needs of patients receiving either moderately or highly emetogenic chemotherapy since it has been demonstrated to increase the control of nausea and vomiting afforded by the association of setrons with dexamethasone.

- Statistically significant and clinically meaningful improvements in complete response rate were achieved in all casopitant treatment groups compared with the control group (setron + dexamethasone); subjects were one third to one half as likely to vomit/retch or use rescue therapy in their first cycle of chemotherapy compared with subjects who received the control regimen.

- Casopitant added to the control regimen is superior to the control regimen alone in the prevention of CINV for initial as well as for repeat cycles of MEC and HEC. The effect observed in cycle 1 persisted across cycles 2 – 4 and the patients continue to derive benefit from casopitant throughout the full duration of chemotherapy.

In HEC, both casopitant treatment groups showed clinically relevant reductions in the severity of nausea compared with the control group. More than half of all casopitant treated subjects experienced no nausea during the first 120 hours of Cycle 1. In the pivotal study, larger proportions of subjects in all casopitant treatment groups reported no impact on daily life of CINV compared with control, supporting an improvement in quality of life for these subjects.

- The effect of casopitant was demonstrated in both sexes.

- The improvement of efficacy of casopitant compared to control and measured with standard techniques over a 5-day period is achieved with minimal additional toxicity related to casopitant.

- This improved efficacy results in better patient reported outcomes.

- Casopitant was effective as a Single Oral 150 mg Dose. This regimen of casopitant for prevention of CINV provides greater convenience for patients and caregivers, compared with a 3-day aprepitant regimen. A 3-Day Oral casopitant regimen was investigated but did not yield substantial benefit over the 1- Day Only dose.

The pivotal studies were large, well controlled, multicentre, and achieved highly significant results in each tested arm. These results were consistent across multiple endpoints, in multiple subsets of subjects and spanned a spectrum of emetogenic stimuli. They were very similar to those obtained in the supportive Phase II studies, providing further evidence of the consistent benefit of casopitant in the prevention of CINV.

Casopitant is applied for in the same indications as aprepitant.

The recommended doses of casopitant, ondansetron and dexamethasone are:

- Highly emetogenic chemotherapy

Day	Oral Casopitant	IV Ondansetron	Oral Dexamethasone
1	150 mg	32 mg	12 mg
2			8 mg X 2
3			8 mg X 2
4			8 mg X 2

- Moderately emetogenic chemotherapy

Day	Oral Casopitant	Oral Ondansetron	IV Dexamethasone
1	150 mg	8 mg x 2	8 mg
2		8 mg X 2	
3		8 mg X 2	

The single 150 mg oral dose of casopitant should be administered 30 to 60 minutes prior to chemotherapy.

In patients receiving moderately emetogenic chemotherapy there remains a major concern as the applicant did not respond satisfactorily to the points below:

- Differences in complete response are mainly driven by positive results in the delayed phase, as no differences between groups were detected in the acute phase.
- The marginal results seen for the primary endpoint are only partially substantiated by secondary endpoints and limited to an effect in vomiting since no differences in nausea have been seen.
- Considering that nausea is the main complaint of patients exposed to chemotherapy, the clinical relevance of the observed effect in the studied population is questioned.

PONV

Superiority was demonstrated for both oral and IV casopitant in combination with ondansetron, over ondansetron alone, for the prevention of PONV in high risk subjects, as measured by complete response during the first 24 hours after surgery. This superiority has been proved for the prevention of vomiting, while the difference was not significant for the prevention of nausea. Casopitant gives no definitive solution for the prevention of late emetic symptoms. Indeed, complete response (no vomiting, no retching, and no use of rescue medications) between 24-48 hours after surgery was not significantly different in the casopitant+ondansetron group and in the ondansetron-alone group.

Therefore, for the prevention of post-discharge nausea and vomiting, there is still need to add a third antiemetic agent such as dexamethasone.

Clinical safety

CINV

The well-characterized safety profile of casopitant is acceptable; adverse events that may be related to the drug are somnolence, sedation, fatigue and dizziness. The overall incidence of reported adverse events was generally comparable across the treatment groups in the phase III studies; the toxicities observed were within expected ranges for subjects receiving AC-MEC and cisplatin-based HEC.

According to the clinical data supplemental cardiac monitoring is not needed when casopitant is administered in the proposed regimens for prevention of CINV.

PONV

The Applicant has provided a table with median (minimum, and maximum) of change from baseline QTcF values by timepoint for the treatment groups in study NKV109990. This summary showed that casopitant itself does not result in QTc prolongation. However, when the group placebo+ketoconazole is compared with the group casopitant+ketoconazole, the median QTc prolongation is slightly higher in the latter than in the former group, especially in the 1-day casopitant dose regimen.

Additional summaries of outlier QTcF values were summarized by the Applicant: change > 30 and < 60 msec; absolute QTcF > 450 msec. The outlier values are infrequent and are generally associated with ketoconazole administration. However, at hours 2, 3 and 4 post-dose there are more patients with change from baseline > 30 msec in the casopitant+ketoconazole group when compared with the placebo+ketoconazole group in the one day-dose regimen. This difference was not seen in the 3-day regimen. Finally, there was no patient with a QTcF value > 450 msec in the casopitant alone group (one day regimen).

These data show that the administration of casopitant alone is not followed by significant QTc prolongation. However, when a strong CYP 3A4 inhibitor is associated with casopitant, significant QTc prolongation can occur. Therefore the administration of strong CYP 3A4 inhibitors is not recommended in patients who have been treated with casopitant.

About cardiotoxicity, the Applicant has analysed the data from studies NKF100096 and NKV102549. The company used an ultra-sensitive (Singulex) assay (LOQ value of 0.2 pg/ml) to measure troponin levels in blood (EDTA) plasma samples retained from a previous long-term dosing study (study NKF100096). The study concerned was an 8-week study, with daily administration of 80-120 mg of casopitant, randomized, double-blind, double-dummy, parallel-group, placebo-controlled forced dose titration study to evaluate the efficacy and safety of casopitant and paroxetine in subjects with major depressive disorder. Casopitant was administered at cumulative exposures 70 times higher than that of one antiemetic cycle of one single dose of casopitant 150 mg. At that dose casopitant did not cause cardiomyocyte damage in humans.

In the other study (NKV102549), troponin data were originally reported. There is no imbalance between treatment arms in the degree of cTnI elevation. These data support the hypothesis that casopitant does not augment anthracycline-induced cardiac toxicity.

Finally, the company has undertaken a thorough analysis of casopitant's clinical cardiac safety profile in both the cancer population and the surgical population. This program was also requested by the FDA, to analyze the cardiac event terms across all 52 casopitant clinical studies. The analyses included 3502 subjects in the non-casopitant group and 6192 subjects receiving at least one dose of casopitant. Three types of symptoms (abnormal cardiac enzymes, myocardial infarctions and ischaemias) have lower incidence within the casopitant groups than in the non-casopitant groups.

In the category “heart failure symptoms”, the preferred term of peripheral oedema comprises the predominant contribution. Peripheral oedema is often associated with the use of doxorubicin and cyclophosphamide in cancer patients. A 4% incidence of oedema can be associated with this treatment regimen in patients treated for metastatic breast cancer. Therefore the difference of incidence for peripheral oedema between the two groups of patients can be caused by the medications used to treat cancer. The other terms more specific for heart failure were balanced across casopitant and non-casopitant groups.

As only the one-day regimen of casopitant remains in the SPC, it is considered that the cardiac toxicity is no longer an issue.

Risk Management plan

Revised EU-RMP: Summary table of proposed pharmacovigilance activities and proposed risk minimisation activities by safety concern

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Neutropenia (CINV)	Routine Pharmacovigilance activities Evaluation of safety information from ongoing study NKV110721	Neutropenia listed as ADR in Section 4.8 (Undesirable Effects) of 150 mg SmPC with cross reference to Section 4.5 (Interaction with other medicinal products) Section 4.4 (Special warnings and precautions for use) will contain warning that coadministration of casopitant with certain chemotherapeutic agents primarily metabolised by CYP3A may result in increased toxicities of these agents Included as adverse event in package leaflet
Hiccups (CINV)	Routine Pharmacovigilance Evaluation of safety information from ongoing study NKV110721	Listed as ADR in Section 4.8 (Undesirable Effects) of 150 mg SmPC and package leaflet
Dizziness	Routine pharmacovigilance Evaluation of safety information from ongoing study NKV110721	Listed as ADR in Section 4.8 (Undesirable Effects) of 50 mg and 150 mg SmPCs Statement in SmPCs Section 4.7 (Effects on ability to drive and use machines) of SmPC and package leaflet
Fatigue (CINV)	Routine pharmacovigilance Evaluation of safety information from ongoing study NKV110721	Listed as ADR in Section 4.8 (Undesirable Effects) of 150 mg SmPC Statement in 150 mg SmPC Section 4.7 (Effects on ability to drive and use machines) of SmPC and package leaflet
Drug interactions	Routine pharmacovigilance Evaluation of interactions with docetaxel (NKV100781) and cyclophosphamide (NKV103444)	Contraindications against use of casopitant in combination with drugs that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with potentially serious and/or life-threatening reactions, such as astemizole, cisapride, pimozide or terfenadine in SmPCs Section 4.3

IV. ORPHAN MEDICINAL PRODUCTS

Not Applicable.

V. BENEFIT RISK ASSESSMENT

RISK/BENEFIT BALANCE

CINV

Casopitant is not intended to substitute setrons or dexamethasone in the prevention of acute and delayed nausea and vomiting induced by highly or moderately emetogenic chemotherapy. It should be combined to the standard antiemetic regimen used at the present time (setron + dexamethasone) to improve the control of emesis as soon as the first chemotherapy course.

One of the unpleasant and distressing side effects of chemotherapy patients fear most is nausea and vomiting because both these effects can significantly deteriorate the quality of life and decrease cognitive and physical functioning. Even a single emetic episode occurring any time during the chemotherapy courses can reduce to nearly nil the chances to avoid emesis during all the further courses. The patient can also be prompted to discontinue the treatment of his/her malignant disease and, as a consequence, lose the benefit of a potentially curative or at least a life significantly prolonging therapy.

It is of prime necessity to give an antiemetic regimen with maximal efficacy from the first and during all the further courses of chemotherapy; once the antiemetic regimens failed, it is nearly impossible to avoid further CINV, no matter which drugs are used.

Despite the major breakthrough the setrons achieved in the prevention of CINV, improvement is still needed, especially in the delayed phases of both HEC and MEC induced nausea and vomiting. As a matter of fact, appropriate doses of any setron result in complete control of emesis in 50 – 70 % of patients during the first 24 hours after administration of high dose cisplatin therapy. Among patients receiving moderately emetogenic regimens, usually cyclophosphamide-based, complete control of emesis ranges from 70 % to 80 %. At this time there are no reliable criteria to predict the efficacy of 5-HT3 receptor antagonists in a particular patient. As the antiemetic regimen must be the most successful from the first time cytostatic agents are given, the physician is not allowed to restrict the use of a new antiemetic drug to those patients who did not derive an adequate control of emesis with the standard setron + dexamethasone regimen given previously.

Efficacy

Casopitant, a novel agent of a new class known as the NK-1 receptor antagonists, meets the persistent clinical needs of patients receiving highly emetogenic chemotherapy since it has been demonstrated to increase the control of nausea and vomiting afforded by the association of setrons with dexamethasone. The results yielded by casopitant confirm the medical importance of NK-1 receptor antagonists as essential components of antiemetic regimens for the prevention of CINV in patients receiving highly emetogenic chemotherapy.

- Statistically significant and clinically meaningful improvements in complete response rate were achieved in all casopitant treatment groups compared with the control group (setron + dexamethasone); subjects were one third to one half as likely to vomit/retch or use rescue therapy in their first cycle of chemotherapy compared with subjects who received the control regimen.
- Casopitant added to the control regimen is superior to the control regimen alone in the prevention of CINV for initial as well as for repeat cycles of HEC. The effect observed in cycle 1 persisted across cycles 2 – 4 and the patients continue to derive benefit from casopitant throughout the full duration of chemotherapy.
- Both casopitant treatment groups showed clinically relevant reductions in the severity of nausea compared with the control group. More than half of all casopitant treated subjects experienced no nausea during the first 120 hours of Cycle 1. In the pivotal study, larger proportions of subjects in all casopitant treatment groups reported no impact on daily life of CINV compared with control, supporting an improvement in quality of life for these subjects.

- The effect of casopitant was demonstrated in both sexes. The improvement of efficacy of casopitant compared to control and measured with standard techniques over a 5-day period is achieved with minimal additional toxicity related to casopitant.
- This improved efficacy results in better patient reported outcomes.
- Casopitant was effective as a Single Oral 150 mg Dose. This regimen of casopitant for prevention of CINV provides greater convenience for patients and caregivers, compared with a 3-day aprepitant regimen. A 3-Day Oral casopitant regimen was investigated but did not yield substantial benefit over the 1- Day Only dose.

The pivotal studies were large, well controlled, multicentre, and achieved highly significant results in each tested arm. These results were consistent across multiple endpoints, in multiple subsets of subjects and spanned a spectrum of emetogenic stimuli. They were very similar to those obtained in the supportive Phase II studies, providing further evidence of the consistent benefit of casopitant in the prevention of CINV.

Casopitant is applied for in the same indications as aprepitant.

The recommended doses of casopitant, ondansetron and dexamethasone are:

Highly emetogenic chemotherapy

Day	Oral Casopitant	IV Ondansetron	Oral Dexamethasone
1	150 mg	32 mg	12 mg
2			8 mg X 2
3			8 mg X 2
4			8 mg X 2

The single 150 mg oral dose of casopitant should be administered 30 to 60 minutes prior to chemotherapy

In patients receiving moderately emetogenic chemotherapy there remains a major concern as the applicant did not respond satisfactorily to the points below:

- Differences in complete response are mainly driven by positive results in the delayed phase, as no differences between groups were detected in the acute phase.
- The marginal results seen for the primary endpoint are only partially substantiated by secondary endpoints and limited to an effect in vomiting since no differences in nausea have been seen.
- Considering that nausea is the main complaint of patients exposed to chemotherapy, the clinical relevance of the observed effect in the studied population is questioned.

Safety

The well characterized safety profile of casopitant is acceptable; adverse events that may be related to the drug are somnolence, sedation, fatigue, dizziness. The overall incidence of reported adverse events was generally comparable across the treatment groups in the phase III studies; the toxicities observed were within expected ranges for subjects receiving AC-MEC and cisplatin-based HEC.

According to the clinical data supplemental cardiac monitoring is not needed when casopitant is administered in the proposed regimens for prevention of CINV.

Conclusion: The risk/benefit balance is favourable in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy.

PONV

Casopitant has proven to exert an additional prophylactic effect on nausea and vomiting in the post-operative phase. Superiority was demonstrated over ondansetron alone for the prevention of PONV in high risk subjects, as measured by complete response during the first 24 hours after surgery. However, casopitant gives no definitive solution for the prevention of late emetic symptoms.

The type of design chosen for the pivotal studies might necessarily lead to a restricted indication: clinical recommendations establish the use of antiemetic drugs in monotherapy (i.e. 5HT3 antagonists or dexamethasone) to prevent PONV and restrict the use of combination therapy (i.e. “setrons” plus dexamethasone or NK-1 antagonists as a second line) to those patients at a very high risk of emesis following surgery. Casopitant is aimed to this subpopulation of patients at high risk of PONV, which in principle might be acceptable. However, a direct comparison to the standard of treatment combination in this clinical setting, i.e. setrons plus dexmethasone, might be desirable.

Safety

The safety profile of casopitant is favourable. No serious neurologic adverse events occurred during the clinical studies. No significant QT prolongation has been observed. However, the risks of using casopitant in patients with (serious) cardiovascular disease, and receiving other drugs such as ondansetron, droperidol, which can prolong the QT interval, could have been underestimated. Significant QTc prolongation has been observed in a clinical study when casopitant was associated to ketoconazole, a strong CYP3A4 inhibitor.

Adverse events that may be related to the drug are somnolence, sedation, fatigue, dizziness. The overall incidence of reported adverse events was generally comparable across the treatment groups in the phase III studies; the toxicities observed were within expected ranges for subjects receiving AC-MEC and cisplatin-based HEC.

Conclusion: The risk/benefit balance is favourable for PONV.