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Casopitant Mesilate

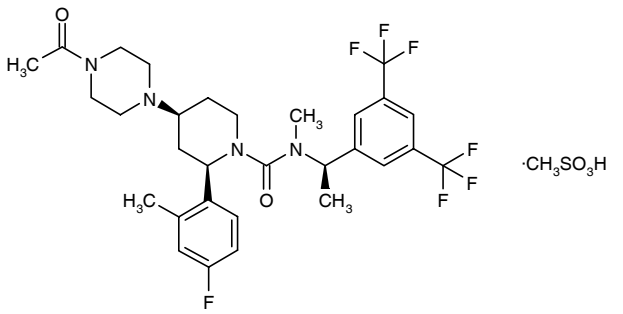
Rec INNM

Tachykinin NK_1 Antagonist
Treatment of Nausea/Vomiting

Casopitant mesylate (USAN)
GW-579769
Rezonic™
Zunrisa™

4(*S*)-(4-Acetylpiperazin-1-yl)-*N*-[1(*R*)-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2(*R*)-(4-fluoro-2-methylphenyl)-*N*-methylpiperidine-1-carboxamide methanesulfonate

InChI=1/C30H35F7N4O2/c1-18-13-24(31)5-6-26(18)27-17-25(40-11-9-39(10-12-40)20(3)42)7-8-41(27)28(43)38(4)19(2)21-14-22(29(32,33)34)16-23(15-21)30(35,36)37/h5-6,13-16,19,25,27H,7-12,17H2,1-4H3/t19-,25+,27-/m1/s1



$C_{13}H_{39}F_7N_4O_5S$
Mol wt: 712.719
CAS: 414910-30-8
CAS: 414910-27-3 (free base)
EN: 320922

Abstract

Casopitant mesilate is a novel, orally active tachykinin NK_1 receptor antagonist. In preclinical pharmacological testing it revealed potent and long-lasting antiemetic effects both alone and in combination with ondansetron in a ferret model using cisplatin as the emetic agent. Both phase II and phase III studies have shown robust antiemetic activity when casopitant was coadministered with ondansetron and dexamethasone, either as a single oral dose or as a 3-day i.v./oral dose regimen, in patients receiving moderately or highly emetogenic chemotherapy. A quality-of-life study showed significant differences in favor of casopitant and standard antiemetic therapy over standard therapy alone in patients receiving highly emetogenic chemotherapy. The addition of casopitant to standard antiemetic therapy was generally well tolerated; the most common adverse events were fatigue, neutropenia, leukopenia and anemia, similar to those on standard antiemetic therapy alone.

Synthesis

Casopitant can be prepared by two related methods starting from either racemic 2-(4-fluoro-2-methylphenyl)-4-piperidinone (I) or from the corresponding (*R*)-enantiomer (II). Optically pure piperidinone (II), obtained either by asymmetric synthesis or by resolution of (I) with L-mandelic acid, is treated with triphosgene and $NaHCO_3$ to give the carbamoyl chloride (III), which is then coupled with *N*-methyl-1(*R*)-[3,5-(bis-trifluoromethyl)phenyl]ethylamine (IV) to afford the urea adduct (V). Alternatively, reaction of racemic piperidinone (I) with triphosgene and DIEA followed by coupling of the resulting carbamoyl chloride (VI) with the 1-aryl-ethylamine (IV) leads to a diastereomeric mixture of urea adducts, from which the target (*R*,*R*)-diastereoisomer (V) can be isolated using flash column chromatography. The *N*-carbamoyl piperidone (V) is then subjected to reductive amination with *N*-acetylpiperazine (VII) in the presence of $NaBH(OAc)_3$ to generate a mixture of epimeric 4-piperazinylpiperidines, from which the 4(*S*)-isomer casopitant is finally obtained through recrystallization as the corresponding methanesulfonate salt (1, 2). Scheme 1.

The intermediate 2-aryl-4-piperidinones (I) and (II) can be obtained by the following methods. Condensation of 2-methyl-4-fluorobenzaldehyde (VIII) with 4-amino-2-butanone ethylene ketal (IX) gives the imine ketal (X), which undergoes Mannich-type cyclization to the 4,4-ethylenedioxy piperidine (XI) upon refluxing in benzene in the presence of anhydrous *p*-TsOH. Subsequent acidic hydrolysis of the ethylene ketal (XI) yields the racemic piperidone (I). In a different strategy, condensation of 4-fluoro-2-methylphenylmagnesium bromide (XII) with 4-methoxypyridine (XIII) in the presence of benzyl chloroformate followed by acidic hydrolysis of the intermediate

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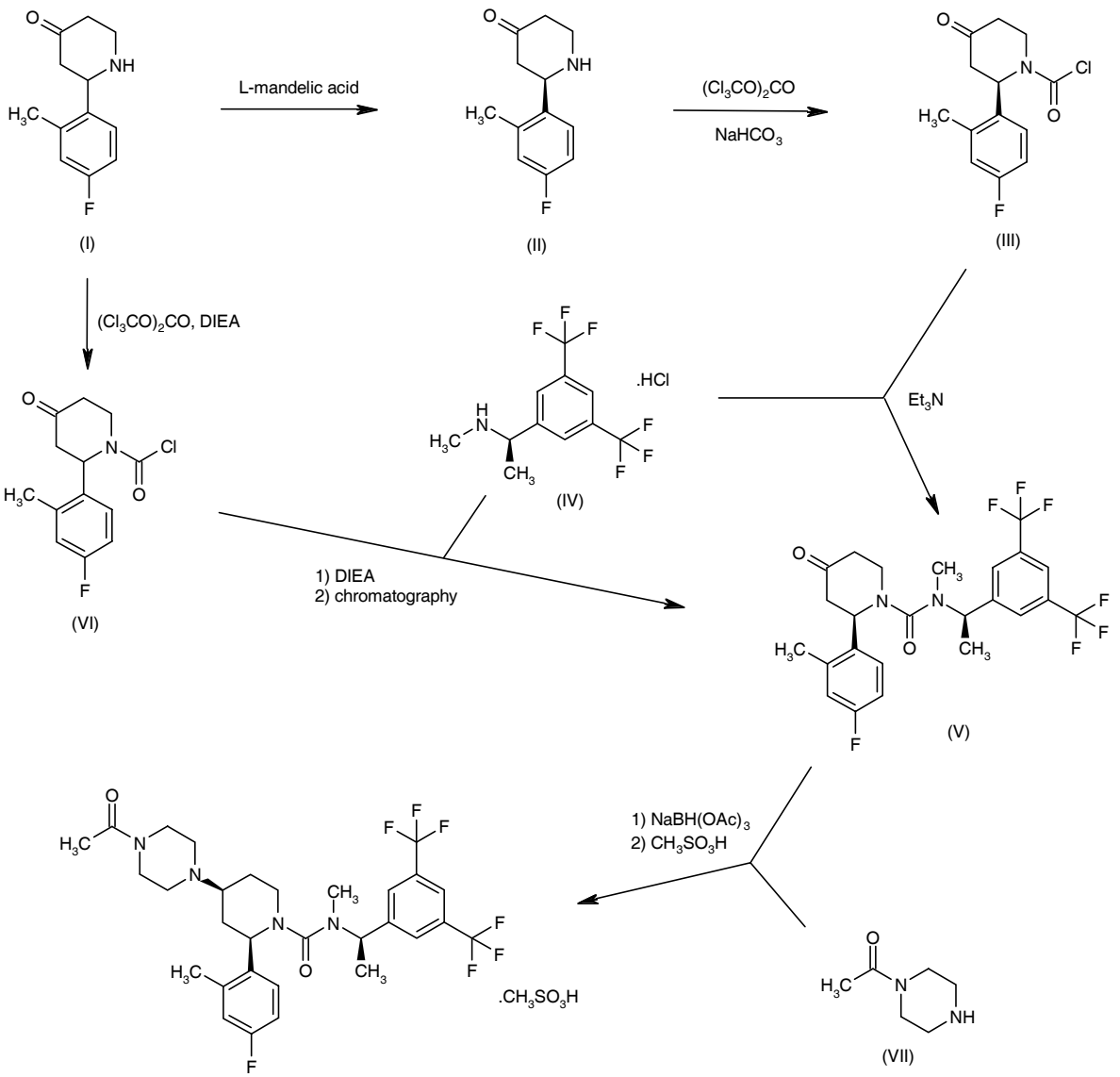
Scheme 1: Synthesis of Casopitant Mesilate

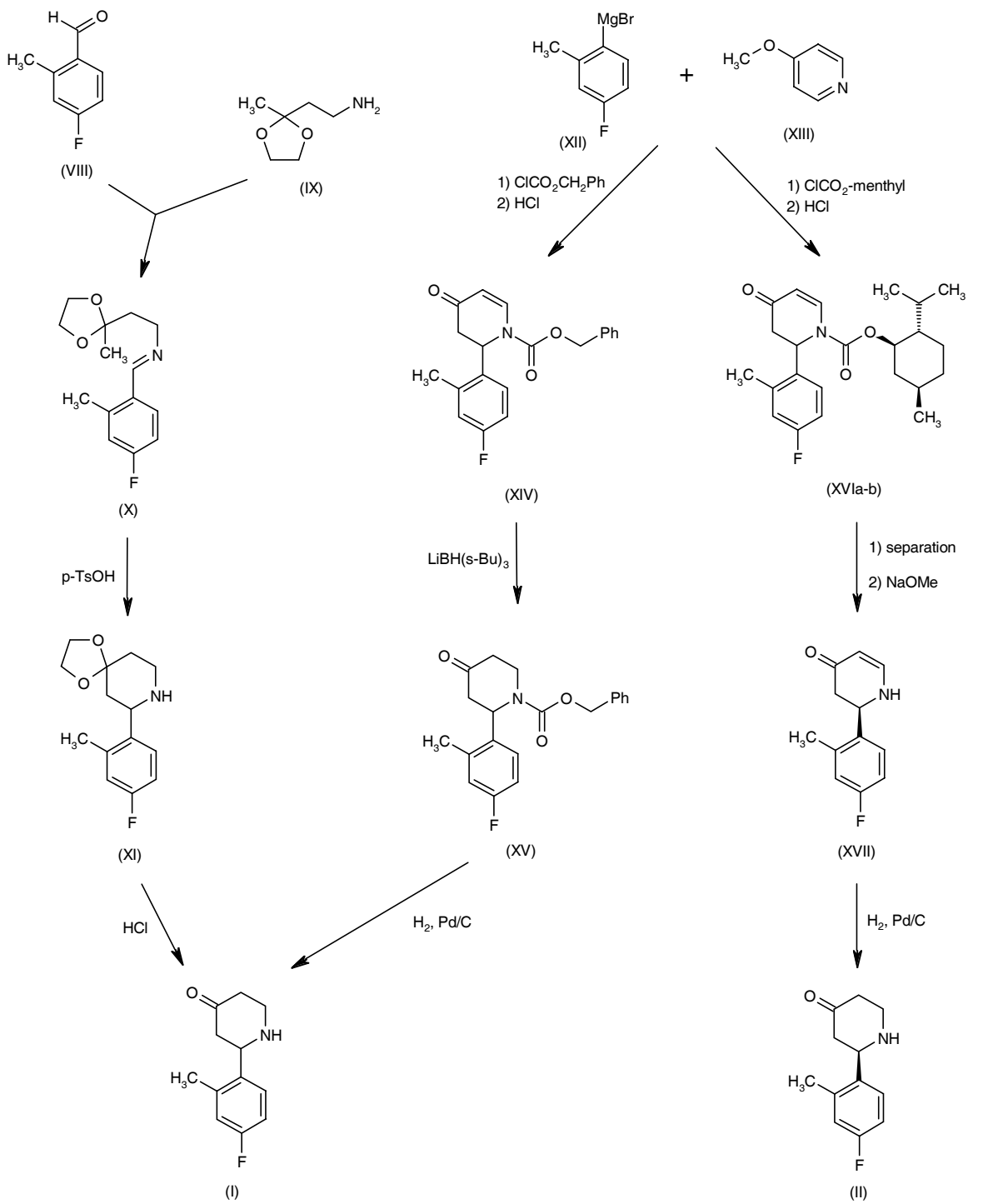


enol ether provides 1-(benzyloxycarbonyl)-2-(4-fluoro-2-methylphenyl)-2,3-dihydro-4-pyridone (XIV). After reduction of (XIV) to the corresponding piperidinone (XV) by means of L-selectride in cold THF, the protecting group is removed by hydrogenolysis over Pd/C to provide the deprotected amine (I) (1, 2). Similarly, condensation of the Grignard reagent (XII) with 4-methoxypyridine (XIII) in the presence of (–)-menthyl chloroformate followed by acidic enol ether hydrolysis gives the dihydropyridone menthyl carbamate (XVIa-b) as a mixture of diastereoisomers, which can be separated by flash column chromatography. The minor 2(*R*)-isomer is then hydrolyzed employing methanolic NaOMe to provide 2(*R*)-(4-fluoro-2-methylphenyl)-2,3-dihydro-4-pyridone (XVII), which is reduced to the chiral piperidinone (II) by catalytic hydrogenation over Pd/C (1). Scheme 2.

Background

Nausea and vomiting are distressing and feared side effects of several cancer therapies and even clinicians and nurses may underestimate their incidence (3). Chemotherapy-induced nausea and vomiting (CINV) seriously impacts on patients' quality of life and may cause them to delay or refuse therapy (4, 5). CINV can affect up to 90% of patients exposed to highly (HEC) and moderately emetogenic chemotherapy (MEC) and it may last up to 5 days or longer. Patients ideally need to be protected

Scheme 2: Synthesis of Intermediates (I) and (II)



throughout this period (6). It is easier to prevent nausea and vomiting than to treat it, but despite prophylaxis with a variety of agents, 40-50% of patients may experience breakthrough nausea and vomiting (5).

Two key pathways and neurotransmitters are thought to underlie the physiology of CINV: a peripheral pathway mediated by serotonin (5-HT) and 5-HT_3 receptors residing primarily in the gut and vagus nerve (7); this is com-

plemented by a central pathway activated by substance P and mediated by tachykinin NK_1 receptors located primarily in the brainstem. These NK_1 receptors control the vomiting reflex, whereas the function of NK_1 receptors elsewhere in the central nervous system (CNS) is less well defined. The recent development of NK_1 antagonists such as aprepitant has improved the treatment of CINV when coadministered with agents such as ondansetron (a 5-HT_3 antagonist) and dexamethasone. Current influential guidelines (6, 8-10) now include aprepitant as part of standard antiemetic therapy for patients receiving HEC or MEC.

Casopitant mesilate (GW-679769, Rezonic™, Zunrisa™) is an NK_1 antagonist which has recently been submitted to the FDA for the prevention of CINV. This review summarizes its preclinical pharmacology, pharmacokinetics, safety and clinical efficacy in CINV.

Preclinical Pharmacology

The binding affinity of casopitant and two of its metabolites (a hydroxylated derivative M1 and a ketone derivative M2) has been evaluated using ferret brain cortical NK_1 receptors (Table I). These values are said to be similar to those found for human NK_1 receptors, although the human data are not currently in the public domain (11). Brief details for three human metabolites of casopitant, including M1 (GSK-525060) and two others, have been published. They all have similar pK_i values for the NK_1 receptor (10.6-10.7). M1 had an ED_{50} of 0.07 mg/kg i.p. in the gerbil foot-tapping model which detects brain-penetrant NK_1 antagonists (12).

In a ferret model of cisplatin-induced acute and delayed emesis, a single i.p. dose of casopitant significantly and dose-dependently inhibited the number of retching and vomiting episodes. The ID_{50} was 80 μg/kg and complete inhibition was obtained at 2 mg/kg in the acute (6 h) model. In the delayed emesis model (72 h), casopitant had an ID_{50} of 1.3 mg/kg for single doses and 0.28 mg/kg for once-daily dosing (13). The potential benefit of combining casopitant with ondansetron was demonstrated in the same model by coadministering suboptimal doses of casopitant and ondansetron (0.3, 0.1 and 0.03 mg/kg i.p.) 25 min before cisplatin (10 mg/kg i.p.) The coadministration of these agents significantly decreased emetic events and nausea-like behaviors compared to monotherapy (14).

Table I: Binding affinities for casopitant and metabolites in ferret brain cortical NK_1 receptor binding assays (data from Ref. 11).

Compound	K_i (pM) (mean ± SD)
Casopitant	163 ± 39
M1	464 ± 132
M2	108 ± 31

Values are based on n = 8.

Pharmacokinetics and Metabolism

Selected pharmacokinetic parameters for oral casopitant 30 and 90 mg together with its hydroxylated metabolite (GSK-525060) were determined in healthy subjects (15) (Table II). The half-life of casopitant does not seem to have been reported in man to date, but in the ferret the mean half-life was 2.75 h after an i.p. dose of 0.3 mg/kg (11). The oral absorption of casopitant (50-150 mg) was rapid, with a lag time of 13 min and an absorption half-time of 16 min. The population estimate of apparent oral clearance was 24.4 l/h/70 kg based on a dose-ranging study in 562 female patients with postoperative nausea and vomiting (PONV) (16). In a pooled analysis of two chemotherapy studies, the apparent estimate of oral clearance was 17.4 l/h/70 kg after oral doses of 50-150 mg casopitant. Age, gender or race did not modify casopitant's pharmacokinetic profile (17).

Safety

A double-blind, placebo-controlled, randomized trial in 69 healthy volunteers demonstrated that the most common adverse events with casopitant 30 and 90 mg p.o. were somnolence (25-27%) and headache (4-9%); the placebo rate was 1% and 3%, respectively, for these events. No serious adverse events occurred (15).

In phase II trials the most common adverse events included nausea (11-28%), fatigue (4-21%), neutropenia (12-18%) and hiccups (0-17%) (18, 19), and in phase III studies the most common adverse events comprised

Table II: Selected pharmacokinetic parameters of oral casopitant and its hydroxylated metabolite (GSK-525060) in healthy volunteers (data from Ref. 15).

Treatment	n	$AUC_{(0-t)}$ ng.h/ml	C_{max} (ng/ml)	Median t_{max} (h) (range)
Casopitant				
Casopitant 30 mg	67	568	144	1.5 (1.5-5.0)
Casopitant 90 mg	68	1912	465	1.5 (1.5-5.0)
GSK-525060 metabolite				
Casopitant 30 mg	67	441	82.8	3.50 (1.5-5.0)
Casopitant 90 mg	68	1478	264	3.50 (1.5-5.0)

AUC, area under the concentration–time curve; C_{max}, peak plasma concentration; t_{max}, time to peak plasma levels (values are geometric means); n, number of subjects.

Table III: Key outcomes from phase II trials of casopitant in CINV (data from Refs. 18, 19).

HEC (18)	n	CR (%)	*P* value
OND 32 mg i.v. + DEX p.o. D1-D4 + placebo = CTRL	84	60	
CTRL + CAS 50 mg p.o. D1-D3	82	76	0.0036
CTRL + CAS 100 mg p.o. D1-D3	81	86	0.0036
CTRL + CAS 150 mg p.o. D1-D3	81	77	0.0036
CTRL + CAS 150 mg p.o. D1	83	75	n/a
CTRL + APR 125 mg p.o. D1 + 80 mg p.o. D2-D3	82	72	n/a
MEC (19)			
OND 8 mg p.o. b.i.d. D1-D3 + DEX 8 mg i.v. D1 + placebo = CTRL	120	70	
CTRL + CAS 50 mg p.o. D1-D3	120	81	0.012
CTRL + CAS 100 mg p.o. D1-D3	121	79	0.012
CTRL + CAS 150 mg p.o. D1-D3	119	85	0.012
CTRL + CAS 150 mg p.o. D1	119	80	n/a
OND 16 mg p.o. D1-D3 + DEX 8 mg i.v. D1 + CAS 150 mg D1-D3	120	84	n/a

CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; CR, complete response (no vomiting/retching; no rescue medications or premature withdrawals); OND, ondansetron; DEX, dexamethasone; CTRL, control; D, day; CAS, casopitant; APR, aprepitant; n/a, not assessed, not included in analysis.

neutropenia, leukopenia, anemia, alopecia, fatigue and constipation (20-23).

Clinical Studies

A phase I positron emission tomography (PET) study showed that oral casopitant can result in 98% NK_1 receptor occupancy for up to 24 h postdose (24).

Two multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group phase II trials were conducted (18, 19) in patients receiving HEC or MEC. The primary outcome in both trials was complete response (CR) during the first 120 h of HEC or MEC (no vomiting/retching; no rescue medications or premature withdrawals). The results are shown in Table III. Each trial comprised six arms as detailed in the table, but arms 5 and 6 were exploratory and not included in the primary analysis. The addition of casopitant to standard ondansetron/dexamethasone therapy in both trials significantly increased the response rate for the primary endpoint. Although not included in the primary analysis, it appeared that oral casopitant given once on day 1 (75% CR) was at least as effective, if not slightly more so, than oral aprepitant given over 3 days (72% CR) (18). Various subanalyses were conducted on these trials; the effects of casopitant were unaffected by cisplatin dose in the HEC trial (25) and by gender (26), taxane use (27) or gastrointestinal cancer and oxaloplatin use (28) in the MEC trial.

Two multinational, double-blind, active-controlled, randomized phase III trials were conducted in patients receiving HEC (20, 21) or MEC (22, 23). The HEC trial used two different dose regimens added onto standard ondansetron/dexamethasone therapy in patients receiving cisplatin. The primary outcome was CR in the first 120 h and the results of the HEC trial are shown in Table IV. The addition of casopitant to either regimen increased the complete response rate by 14-20% over ondansetron/dexamethasone alone. Significant differences were seen on the other parameters and this effect was maintained over 5 other cycles of chemotherapy (CR 56-97% with standard therapy *vs.* 91-100% with casopitant 150 mg and 60-89% with i.v./oral casopitant) (20, 21). Moreover, in this trial a quality-of-life evaluation using the Functional Living Index-Emesis (FLIE) questionnaire was performed. Patients completed the FLIE at baseline, before chemotherapy and on day 6 after completion of the first HEC cycle. When the individual FLIE questions were assessed, a greater proportion (8-18%) of casopitant-treated patients had No Impact on Daily Living (NIDL) responses for all domains compared to controls ($P < 0.05$). The nausea domain NIDL ranges were 59.4-70.5%, 73.5-79.6% and 70.9-80.4%, respectively, for the control group and the groups receiving single oral doses of casopitant and 3-day i.v./oral casopitant. For the vomiting domains, the respective values were 72.3-75%, 88.1-93.1% and 87.2-89.8% (29).

With MEC, the addition of casopitant significantly increased the complete response rate by 14-15% over ondansetron/dexamethasone alone and significant differences were seen on the other parameters evaluated, apart from acute vomiting at 0-24 h. However, the response rate in both control and casopitant groups was still high for this parameter. The CR rate was maintained over another 3 cycles (63-69% for control, 79-82% for casopitant 150 mg and 81-84% for i.v./oral casopitant) (22, 23).

Drug Interactions

Casopitant is a mild to moderate inhibitor of cytochrome P-450 CYP3A4 and a moderate inducer of CYP2C9 in cultured human hepatocytes (GSK data on file). As these isoenzymes play a role in (*R*)- and (*S*)- warfarin metabolism, respectively, a drug interaction study was conducted to investigate whether casopitant modified warfarin's pharmacokinetic profile in healthy volunteers. Steady-state, average and maximum INR (interna-

Table IV: Key outcomes from phase III trials of oral and i.v. casopitant in patients receiving highly emetogenic (HEC) or moderately emetogenic chemotherapy (MEC) (data from Refs. 20-23).

	HEC (20, 21)		
Endpoints	CTRL + placebo (n = 265) (%)	CTRL + CAS 150 mg p.o. D1 (n = 266) (%)	CTRL + CAS 90 mg i.v. D1/50 mg p.o. D2-D3 (n = 269) (%)
CR (0-120 h)	66	86*	80**
Acute (0-24 h)	88	95***	94+
Delayed (24-120 h)	66	86*	80**
No vomiting	68	89*	83*
No significant nausea	69	78++	76 NS
No nausea	46	57#	55##
	MEC (22, 23)		
	CTRL + placebo (n = 479) (%)	CTRL + CAS 90 mg i.v. D1 + 50 mg p.o. D2-D3 (n = 479) (%)	CTRL + CAS 150 mg p.o. D1 + 50 mg p.o. D2-D3 (n = 480) (%)
CR (0-120 h)	59	74*	73*
Acute (0-24 h)	85	86 NS	89 NS
Delayed (24-120 h)	59	74*	73*
No vomiting	63	78*	81*

CR, complete response (no vomiting/retching; no rescue medications or premature withdrawals); CTRL, control, standard treatment with ondansetron (OND)/dexamethasone (DEX) (for MEC this was: DEX 8 mg i.v. D1 + OND 8 mg b.i.d. p.o. D1-D3; for HEC this was: OND 32 mg i.v. + DEX 20 mg p.o. D1); CAS, casopitant (the oral CAS 150 mg arm received OND 32 mg i.v. + DEX 8 mg p.o. b.i.d. D2-D4; the i.v. CAS arm also received OND 32 mg i.v. + DEX 12 mg p.o. D1 + DEX 8 mg p.o. once daily D2-D4); D, day; NS, not significant. $^{*}P < 0.0001$; $^{**}P < 0.0004$; $^{***}P = 0.0044$; $^{+}P = 0.0165$; $^{++}P < 0.0272$; $^{\#}P < 0.0105$; $^{\#\#}P = 0.0356$.

tional normalized ratio) values were not significantly affected by 1-3 days of cotherapy with casopitant or multiple dosing with casopitant 60 mg/day for up to 14 days. Additional INR monitoring is thus not required with these regimens of casopitant for patients on warfarin (30).

An open-label, repeated-dose, randomized, crossover study investigated the potential interactions between casopitant (150 mg/day for 3 days) and i.v. cyclophosphamide (500-700 mg/m^2). Interim results suggested that no significant interaction occurs and the pharmacokinetics of cyclophosphamide and its 4-hydroxy metabolite were unaltered. This metabolite requires CYP2B6, CYP3A4 and CYP2C9 isoenzymes for its production from cyclophosphamide (31).

An open-label, two-part, fixed-sequence study in 40 healthy volunteers assessed the effects of oral casopitant on the pharmacokinetics of ondansetron and dexamethasone. The same dosing regimens as those used in the phase III studies were investigated. Ondansetron exposure was not significantly affected by casopitant. When repeated oral doses of dexamethasone were coadministered with repeated doses of casopitant, the AUC for dexamethasone increased by 39% and 108%, respectively, on days 1 and 3. However, no reduction in dexamethasone dose was considered necessary when casopitant was coadministered with a single i.v. dose of dexamethasone (32).

An open-label, multipart, two-period, single-sequence study investigated the effects of oral casopitant on the pharmacokinetics of oral granisetron or oral dolasetron in 37 healthy volunteers. Single- and repeated-dose casopitant had no effects on the exposure of coadministered granisetron. Small changes in the exposure to hydrodolasetron, the active metabolite of dolasetron, were observed with coadministration of casopitant; however, these changes were not believed to be clinically relevant (33).

Conclusions

Casopitant appears to be an effective and well-tolerated NK_1 receptor antagonist. Its clinical potential has been demonstrated in both MEC and HEC regimens, and moreover, its efficacy is seen over several treatment cycles and is independent of gender, cisplatin dose and taxane use. The efficacy of casopitant as a single dose added to standard therapy is also encouraging and deserves further study. Although preliminary data suggest that casopitant may be as effective as or even slightly more effective than aprepitant, further work will be needed to corroborate these findings.

Casopitant would seem to be a very useful addition to the oncologist's armamentarium to allow patients to successfully complete their chemotherapy regimens with minimal disruption due to CINV.

Source

GlaxoSmithKline.

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