הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך 13/02/2017

שם תכשיר באנגלית ומספר הרישום Kalydeco 150mg 153-89-34269-00/01/02/03

שם בעל הרישום Vertex Pharmaceuticals (U.K.) Limited

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Posology *Adults, adolescents and children aged 6 years and older and weighing 25 kg or more* The recommended dose of Kalydeco tablets is 150 mg taken orally every 12 hours (300 mg total daily dose) with fat-containing food.	Posology *Adults, adolescents and children aged 6 years and older* The recommended dose of Kalydeco tablets is 150 mg taken orally every 12 hours (300 mg total daily dose) with fat-containing food.	**4.2 Posology and method of administration**
Paediatric population The safety and efficacy of Kalydeco in children aged less than ~~6~~ 2 years have not been established. No data are available. An appropriate dose for children under 6 years of age and weighing less than25 kg cannot be achieved with Kalydeco tablets.	*Paediatric population* The safety and efficacy of Kalydeco in children aged less than 6 years have not been established. No data are available.	**4.2 Posology and method of administration**

Pregnancy There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of ivacaftor in pregnant women.~~No adequate and well-controlled studies of Kalydeco in pregnant women have been conducted~~. Developmental toxicity studies have been performed in rats and rabbits at daily ~~doses~~ exposures ~~up to~~ approximately 5 times (based on the summed AUCs for ivacaftor and its major metabolites) and 11 times (based on the AUC for ivacaftor), respectively, the exposure in humans at the maximum recommended human ~~daily~~ dose (MRHD) and have revealed no evidence of harm to the foetus due to ivacaftor (see section 5.3). As a precautionary measure, it is recommended to avoid the use of ivacaftor during pregnancy unless the clinical condition of the mother requires treatment with ivacaftor. ~~Because animal reproduction studies are not always predictive of human response, Kalydeco should be used during pregnancy only if clearly needed.~~ Breast-feeding It is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of ~~Ivacaftor~~ ivacaftor ~~was shown to be excreted~~ into the milk of lactating female rats. As such, risks to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ivacaftor therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother. ~~The safe use of Kalydeco during breast-feeding has not been established. Kalydeco should only be used during breast-feeding if the potential benefit outweighs the potential risk.~~	Pregnancy .No adequate and well-controlled studies of Kalydeco in pregnant women have been conducted. Developmental toxicity studies have been performed in rats and rabbits at daily doses up to 5 times the human daily dose and have revealed no evidence of harm to the foetus due to ivacaftor (see section 5.3). Because animal reproduction studies are not always predictive of human response, Kalydeco should be used during pregnancy only if clearly needed. Breast-feeding It is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Ivacaftor was shown to be excreted into the milk of lactating female rats. The safe use of Kalydeco during breast-feeding has not been established. Kalydeco should only be used during breast-feeding if the potential benefit outweighs the potential risk.	**4.6 Fertility, pregnancy and lactation**

Fertility Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (resulting in exposures approximately ~~5~~ 8 and ~~6~~ 5 times, respectively, the exposure in humans at the ~~maximum recommended human dose~~ ~~[~~MRHD~~]~~ based on summed AUCs of ivacaftor and its major metabolites) when dams were dosed prior to and during early pregnancy (see section 5.3). No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (resulting in exposures approximately 6 and 3 times respectively, the exposure in humans at the MRHD based on summed AUCs of ivacaftor and its major metabolites).	Fertility Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (resulting in exposures approximately 5 and 6 times, respectively, the exposure in humans at the maximum recommended human dose [MRHD] based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy (see section 5.3). No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (resulting in exposures approximately 3 times the exposure in humans at the MRHD based on summed AUCs of ivacaftor and its metabolites).	
Summary of the safety profile The most common adverse reactions experienced by patients aged 6 years and older who received ivacaftor in the pooled 48-week placebo-controlled Phase 3 studies that occurred with an incidence of at least 3% and up to 9% higher than in the placebo arm were headache (23.9%), oropharyngeal pain (22.0%), upper respiratory tract infection (22.0%), nasal congestion (20.2%), abdominal pain (15.6%), nasopharyngitis (14.7%), diarrhoea (12.8%), dizziness (9.2%), rash (12.8%) and bacteria in sputum (12.8%). Transaminase elevations occurred in 12.8% of ivacaftor-treated patients versus 11.5% of placebo-treated patients. In patients aged 2 to less than 6 years the most common adverse reactions were nasal congestion (26.5%), upper respiratory tract infection (23.5%), transaminase elevations (14.7%), rash (11.8%), and bacteria in sputum (11.8%).	Summary of the safety profile The most common adverse reactions experienced by patients aged 6 years and older who received ivacaftor in the pooled 48-week placebo-controlled Phase 3 studies that occurred with an incidence of at least 3% and up to 9% higher than in the placebo arm were headache (23.9%), oropharyngeal pain (22.0%), upper respiratory tract infection (22.0%), nasal congestion (20.2%), abdominal pain (15.6%), nasopharyngitis (14.7%), diarrhoea (12.8%), dizziness (9.2%), rash (12.8%) and bacteria in sputum (12.8%). Transaminase elevations occurred in 12.8% of ivacaftor-treated patients versus 11.5% of placebo-treated patients. Serious adverse reactions in patients who received ivacaftor included abdominal pain and transaminase elevations (see section 4.4).	**4.8 Undesirable effects**

Serious adverse reactions in patients who received ivacaftor included abdominal pain and transaminase elevations (see section 4.4).

Tabulated list of adverse reactions

Table 1 reflects the adverse reactions observed with ivacaftor in clinical trials (placebo-controlled and uncontrolled studies) in which the length of exposure to ivacaftor ranged from 16 weeks to 144 weeks. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions in ivacaftor-treated patients aged ~~6~~ 2 years and older

System organ class	Adverse reactions	Frequency
Infections and infestations	Upper respiratory tract infection	very common
	Nasopharyngitis	very common
	Rhinitis	common
Nervous system disorders	Headache	very common
	Dizziness	very common
Ear and labyrinth disorders	Ear pain	common
	Ear discomfort	common
	Tinnitus	common

Tabulated list of adverse reactions

Table 1 reflects the adverse reactions observed with ivacaftor in clinical trials (placebo-controlled and uncontrolled studies) in which the length of exposure to ivacaftor ranged from 16 weeks to 144 weeks. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions in ivacaftor-treated patients aged 6 years and older

System organ class	Adverse reactions	Frequency
Infections and infestations	Upper respiratory tract infection	very common
	Nasopharyngitis	very common
	Rhinitis	common
Nervous system disorders	Headache	very common
	Dizziness	very common
Ear and labyrinth disorders	Ear pain	common
	Ear discomfort	common
	Tinnitus	common

	Tympanic membrane hyperaemia	common
	Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	very common
	Nasal congestion	very common
	Sinus congestion	common
	Pharyngeal erythema	common
Gastrointestinal disorders	Abdominal pain	very common
	Diarrhoea	very common
Hepatobiliary disorders	Transaminase elevations	very common
Skin and subcutaneous tissue disorders	Rash	very common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation	uncommon
	Gynaecomastia	uncommon
	Nipple disorder	uncommon
	Nipple pain	uncommon
Investigations	Bacteria in sputum	very common

Description of selected adverse reactions

Laboratory abnormalities

Transaminase elevations

	Tympanic membrane hyperaemia	common
	Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	very common
	Nasal congestion	very common
	Sinus congestion	common
	Pharyngeal erythema	common
Gastrointestinal disorders	Abdominal pain	very common
	Diarrhoea	very common
Hepatobiliary disorders	Transaminase elevations	very common
Skin and subcutaneous tissue disorders	Rash	very common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation	uncommon
	Gynaecomastia	uncommon
	Nipple disorder	uncommon
	Nipple pain	uncommon
Investigations	Bacteria in sputum	very common

Description of selected adverse reactions

Laboratory abnormalities

Transaminase elevations

During the 48-week placebo-controlled studies 1 and 2 in patients aged 6 years and older, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 3.7%, 3.7% and 8.3% in ivacaftor-treated patients and 1.0%, 1.9% and 8.7% in placebo-treated patients, respectively. Two patients, one on placebo and one on ivacaftor, permanently discontinued treatment for elevated transaminases, each >8 x ULN. No ivacaftor-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >1.5 x ULN. In ivacaftor-treated patients, most transaminase elevations up to 5 x ULN resolved without treatment interruption. Ivacaftor dosing was interrupted in most patients with transaminase elevations >5 x ULN. In all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4). Paediatric population The safety data were evaluated in 34 patients between 2 to less than 6 years of age, 61 patients between 6 to less than 12 years of age and 94 patients between 12 to less than 18 years of age. The safety profile is generally consistent among children and adolescents and is also consistent with adult patients. During the 24-week open label Phase 3 clinical study in 34 patients aged 2 to less than 6 years (study 7), the incidence of patients experiencing transaminase elevations (ALT or AST) > 3 x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels > 8 x ULN, which returned to baseline levels following interruption of dosing with ivacaftor granules. Ivacaftor was	During the 48-week placebo-controlled studies 1 and 2 in patients aged 6 years and older, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 3.7%, 3.7% and 8.3% in ivacaftor-treated patients and 1.0%, 1.9% and 8.7% in placebo-treated patients, respectively. Two patients, one on placebo and one on ivacaftor, permanently discontinued treatment for elevated transaminases, each >8 x ULN. No ivacaftor-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >1.5 x ULN. In ivacaftor-treated patients, most transaminase elevations up to 5 x ULN resolved without treatment interruption. Ivacaftor dosing was interrupted in most patients with transaminase elevations >5 x ULN. In all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4). Paediatric population The safety data were evaluated in 61 patients between 6 to less than 12 years of age and 94 patients between 12 to less than 18 years of age. The safety profile is generally consistent among children and adolescents and is also consistent with adult patients. In children aged 6 to less than 12 years, the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 15.0% (6/40) in ivacaftor-treated patients and 14.6% (6/41) in patients who received placebo. A single ivacaftor-treated patient (2.5%) in this age range had an elevation of ALT and AST >8 x ULN. Peak LFT (ALT or AST) elevations were	

permanently discontinued in one patient. In children aged 6 to less than 12 years, the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 15.0% (6/40) in ivacaftor-treated patients and 14.6% (6/41) in patients who received placebo. A single ivacaftor-treated patient (2.5%) in this age range had an elevation of ALT and AST >8 x ULN. Peak LFT (ALT or AST) elevations were generally higher in paediatric patients than in older patients. In almost all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4). Cases suggestive of positive rechallenge were observed.	generally higher in paediatric patients than in older patients. In almost all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4).	
The pharmacokinetics of ivacaftor are similar between healthy adult volunteers and patients with CF. After oral administration of a single 150 mg dose to healthy volunteers in a fed state, the mean (±SD) for AUC and C_{max} were 10600 (5260) ng*hr/mL and 768 (233) ng/mL, respectively. After every 12-hour dosing, steady-state plasma concentrations of ivacaftor were reached by Days 3 to 5, with an accumulation ratio ranging from 2.2 to 2.9. <u>Absorption</u> Following multiple oral dose administrations of ivacaftor, the exposure of ivacaftor generally increased with dose from 25 mg every 12 hours to 450 mg every 12 hours. The exposure of ivacaftor increased approximately 2.5- to 4-fold when given with food containing fat. Therefore, ivacaftor should be administered with fat-containing food. The median (range) t_{max} is approximately	The pharmacokinetics of ivacaftor are similar between healthy adult volunteers and patients with CF. After oral administration of a single 150 mg dose to healthy volunteers in a fed state, the mean (±SD) for AUC and C_{max} were 10600 (5260) ng*hr/mL and 768 (233) ng/mL, respectively. After every 12-hour dosing, steady-state plasma concentrations of ivacaftor were reached by Days 3 to 5, with an accumulation ratio ranging from 2.2 to 2.9. <u>Absorption</u> Following multiple oral dose administrations of ivacaftor, the exposure of ivacaftor generally increased with dose from 25 mg every 12 hours to 450 mg every 12 hours. The exposure of ivacaftor increased approximately 2.5- to 4-fold when given with food containing fat. Therefore, ivacaftor should be administered with fat-containing food. The median (range) t_{max} is	**5.2 Pharmacokinetic properties**

4.0 (3.0; 6.0) hours in the fed state. Ivacaftor granules (2 x 75 mg sachets) had similar bioavailability as the 150 mg tablet when given with fat-containing food to healthy adult subjets. The geometric least squares mean ratio (90% CI) for the granules relative to tablets was 0.951 (0.839, 1.08) for $AUC_{0-\infty}$ and 0.918 (0.750, 1.12) for $C_{max.}$ The effect of food on ivacaftor is similar for both formulations, i.e. tablets or granules. <u>Distribution</u> Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells. After oral administration of 150 mg every 12 hours for 7 days in healthy volunteers in a fed state, the mean (±SD) apparent volume of distribution was 353 (122) L. <u>Biotransformation</u> Ivacaftor is extensively metabolised in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolised by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active. <u>Elimination</u> Following oral administration, the majority of ivacaftor (87.8%) was eliminated in the faeces after metabolic conversion. The major	approximately 4.0 (3.0; 6.0) hours in the fed state. <u>Distribution</u> Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells. After oral administration of 150 mg every 12 hours for 7 days in healthy volunteers in a fed state, the mean (±SD) apparent volume of distribution was 353 (122) L. <u>Biotransformation</u> Ivacaftor is extensively metabolised in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolised by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active. <u>Elimination</u> Following oral administration, the majority of ivacaftor (87.8%) was eliminated in the faeces after metabolic conversion. The	

metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent. The apparent terminal half-life was approximately 12 hours following a single dose in the fed state. The apparent clearance (CL/F) of ivacaftor was similar for healthy patients and patients with CF. The mean (±SD) CL/F for a single 150 mg dose was 17.3 (8.4) L/hr in healthy patients. <u>Dose/time proportionality</u> The pharmacokinetics of ivacaftor are generally linear with respect to time or dose ranging from 25 mg to 250 mg. <u>Hepatic impairment</u> Following a single dose of 150 mg of ivacaftor, patients with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max} (mean [±SD] of 735 [331] ng/mL) but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ (mean [±SD] of 16800 [6140] ng*hr/mL) compared with healthy patients matched for demographics. Simulations for predicting the steady-state exposure of ivacaftor showed that by reducing the dosage from 150 mg q12h to 150 mg once daily, patients with moderate hepatic impairment would have comparable steady-state C_{min} values as those obtained with a dose of 150 mg q12h in patients without hepatic impairment. Therefore in patients with moderate hepatic impairment, a reduced dose of 150 mg once daily is recommended. The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than two-fold.	major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent. The apparent terminal half-life was approximately 12 hours following a single dose in the fed state. The apparent clearance (CL/F) of ivacaftor was similar for healthy patients and patients with CF. The mean (±SD) CL/F for a single 150 mg dose was 17.3 (8.4) L/hr in healthy patients. <u>Dose/time proportionality</u> The pharmacokinetics of ivacaftor are generally linear with respect to time or dose ranging from 25 mg to 250 mg. <u>Hepatic impairment</u> Following a single dose of 150 mg of ivacaftor, patients with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max} (mean [±SD] of 735 [331] ng/mL) but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ (mean [±SD] of 16800 [6140] ng*hr/mL) compared with healthy patients matched for demographics. Simulations for predicting the steady-state exposure of ivacaftor showed that by reducing the dosage from 150 mg q12h to 150 mg once daily, patients with moderate hepatic impairment would have comparable steady-state C_{min} values as those obtained with a dose of 150 mg q12h in patients without hepatic impairment. Therefore in patients with moderate hepatic impairment, a reduced dose of 150 mg once daily is recommended. The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than two-fold.	

Therefore, no dose adjustment is necessary for patients with mild hepatic impairment. Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C, score 10 to 15) but exposure is expected to be higher than in patients with moderate hepatic impairment. The use of ivacaftor in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such cases, the starting dose should be 150 mg every other day. Dosing intervals should be modified according to clinical response and tolerability (see sections 4.2 and 4.4). <u>Renal impairment</u> Pharmacokinetic studies have not been performed with ivacaftor in patients with renal impairment. In a human pharmacokinetic study, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine). There was negligible urinary excretion of ivacaftor as unchanged parent (less than 0.01% following a single oral dose of 500 mg). Therefore, no dose adjustments are recommended for mild and moderate renal impairment. However, caution is recommended when administering ivacaftor to patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see sections 4.2 and 4.4). <u>Paediatric population</u> ~~Non-compartmental analysis of sparse PK samples collected in Phase 3 studies demonstrate an apparent (oral) clearance (CL/F) that was lower in children than in adults and resulted in~~	Therefore, no dose adjustment is necessary for patients with mild hepatic impairment. Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C, score 10 to 15) but exposure is expected to be higher than in patients with moderate hepatic impairment. The use of ivacaftor in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such cases, the starting dose should be 150 mg every other day. Dosing intervals should be modified according to clinical response and tolerability (see sections 4.2 and 4.4). <u>Renal impairment</u> Pharmacokinetic studies have not been performed with ivacaftor in patients with renal impairment. In a human pharmacokinetic study, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine). There was negligible urinary excretion of ivacaftor as unchanged parent (less than 0.01% following a single oral dose of 500 mg). Therefore, no dose adjustments are recommended for mild and moderate renal impairment. However, caution is recommended when administering ivacaftor to patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see sections 4.2 and 4.4). <u>Paediatric population</u> Non-compartmental analysis of sparse PK samples collected in Phase 3 studies demonstrate an apparent (oral) clearance (CL/F)	

~~approximately 47% to 58% higher AUC_{0-12} and 35% to 46% higher C_{trough} in children 6 to <12 years old relative to adults (Table 5). Due to sparse PK sampling ivacaftor volume of distribution and half-life cannot be calculated.~~

~~**Table 5. Mean (SD) steady-state ivacaftor PK parameters following ivacaftor 150 mg every 12 h**~~

~~Population~~	~~*G551D*~~			~~Non-*G551D*~~		
~~Study~~	~~Study 1~~		~~Study 2~~	~~Study 5~~		
~~Age group (years)~~	~~≥18~~	~~12 to <18~~	~~6 to <12~~	~~≥18~~	~~12 to <18~~	~~6 to <12~~
~~N~~	~~60[a]~~	~~14[b]~~	~~26~~	~~19~~	~~11~~	~~8~~
~~C_{max} (ng/mL)~~	~~1310 (658)~~	~~1010 (530)~~	~~2030 (1030)~~	~~1450 (720)~~	~~1370 (741)~~	~~2350 (1500)~~
~~AUC_{0-12} (ng.h/mL)~~	~~11800 (6570)~~	~~8220 (5820)~~	~~17400 (10900)~~	~~13500 (7350)~~	~~12200 (6750)~~	~~21300 (13700)~~
~~C_{trough} (ng/mL)~~	~~773 (544)~~	~~545 (492)~~	~~1040 (874)~~	~~962 (587)~~	~~853 (542)~~	~~1400 (934)~~
~~CL_{ss}/F (L/h)~~	~~17.3 (11.6)~~	~~30.8 (26.4)~~	~~12.4 (7.63)~~	~~14.3 (7.27)~~	~~16.9 (9.78)~~	~~10.9 (9.01)~~

~~[a] N=63 for C_{max}; [b] N=17 for C_{max}~~

~~Note: PK sampling in studies 1 and 2 was conducted at Week 24 and included pre-dose, 1.5, 3, 4, and 6-hour post-dose samples; PK sampling for study 5 was conducted at Week 2 or Week 14 and included pre-dose, 1, 2, 3, 4, and 6 to 8-hour post-dose samples. The pre-dose sample was recycled and used for C_{12} for the estimation of AUC_{0-12}; as such, AUC_{0-12} values are considered approximate.~~

Predicted ivacaftor exposure based on observed ivacaftor concentrations in Phase 2 and 3 studies as determined using population PK analysis is presented by age group in Table 5. Exposures in 6- to 11-year-olds are predictions based on simulations from the population PK model using data obtained for this age group.

that was lower in children than in adults and resulted in approximately 47% to 58% higher AUC_{0-12} and 35% to 46% higher C_{trough} in children 6 to <12 years old relative to adults (Table 5). Due to sparse PK sampling ivacaftor volume of distribution and half-life cannot be calculated.

Table 5. Mean (SD) steady-state ivacaftor PK parameters following ivacaftor 150 mg every 12 h

Population	***G551D***			**Non-*G551D***		
Study	**Study 1**		**Study 2**	**Study 5**		
Age group (years)	**≥18**	**12 to <18**	**6 to <12**	**≥18**	**12 to <18**	**6 to <12**
N	60[a]	14[b]	26	19	11	8
C_{max} (ng/mL)	1310 (658)	1010 (530)	2030 (1030)	1450 (720)	1370 (741)	2350 (1500)
AUC_{0-12} (ng.h/mL)	11800 (6570)	8220 (5820)	17400 (10900)	13500 (7350)	12200 (6750)	21300 (13700)
C_{trough} (ng/mL)	773 (544)	545 (492)	1040 (874)	962 (587)	853 (542)	1400 (934)
CL_{ss}/F (L/h)	17.3 (11.6)	30.8 (26.4)	12.4 (7.63)	14.3 (7.27)	16.9 (9.78)	10.9 (9.01)

[a] N=63 for C_{max}; [b] N=17 for C_{max}

Note: PK sampling in studies 1 and 2 was conducted at Week 24 and included pre-dose, 1.5, 3, 4, and 6-hour post-dose samples; PK sampling for study 5 was conducted at Week 2 or Week 14 and included pre-dose, 1, 2, 3, 4, and 6 to 8-hour post-dose samples. The pre-dose sample was recycled and used for C_{12} for the estimation of AUC_{0-12}; as such, AUC_{0-12} values are considered approximate.

Table 5. Mean (SD) ivacaftor exposure by age group **Age group** | **Dose** | **$C_{min, ss}$ (ng/mL)** | **$AUC_{\tau, ss}$ (ng.h/mL)** 2- to 5-year-olds (<14 kg) | 50 mg q12h | 577 (317) | 10500 (4260) 2- to 5-year-olds (≥14 kg to <25 kg) | 75 mg q12h | 629 (296) | 11300 (3820) 6- to 11-year-olds (≥14 kg to <25 kg) | 75 mg q12h | 641 (329) | 10760 (4470) 6- to 11-year-olds (≥25 kg) | 150 mg q12h | 958 (546) | 15300 (7340) 12- to 17-year-olds | 150 mg q12h | 564 (242) | 9240 (3420) Adults (≥18 years old) | 150 mg q12h | 701 (317) | 10700 (4100) Elderly population Clinical studies of ivacaftor did not include patients aged 65 years and older. Thus, the efficacy and safety of ivacaftor in elderly patients have not been established. Gender The effect of gender on ivacaftor pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of ivacaftor. No dose adjustments are necessary based on gender.	Elderly population Clinical studies of ivacaftor did not include patients aged 65 years and older. Thus, the efficacy and safety of ivacaftor in elderly patients have not been established. Gender The effect of gender on ivacaftor pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of ivacaftor. No dose adjustments are necessary based on gender.	
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Ivacaftor produced a concentration-dependent inhibitory effect on	Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Ivacaftor produced a concentration-dependent inhibitory effect	**5.3 Preclinical safety data**

hERG (human ether-a-go-go related gene) tail currents, with an IC_{15} of 5.5 µM, which is comparable to the C_{max} (5.0 µM) for ivacaftor at the therapeutic dosage. However, no ivacaftor-induced QT prolongation was observed in a dog telemetry study at single doses of up to 60 mg/kg or in ECG measurements from repeat-dose studies of up to 1 year's duration at the 60 mg/kg/day dose level in dogs (C_{max} after 365 days = 36.2 to 47.6 µM). Ivacaftor produced a dose-related but transient increase in blood pressure parameters in dogs at single oral doses of up to 60 mg/kg. Ivacaftor did not cause reproductive system toxicity in male and female rats at 200 and 100 mg/kg/day, respectively. In females, dosages above this were associated with reductions in the overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in the oestrous cycle. In males, slight decreases of the seminal vesicle weights were observed. Ivacaftor was not teratogenic when orally dosed to pregnant rats and rabbits during the organogenesis stage of foetal development at doses resulting in exposures approximately ~~6~~ 5 times (based on the summed AUCs for ivacaftor and its major metabolites) and ~~12~~ 11 times (based on the AUC for ivacaftor), respectively, the exposure in humans at the MRHD~~therapeutic dose, respectively.~~ At maternally toxic doses in rats, ivacaftor produced reductions in foetal body weight and an increase in the incidence of cervical ribs, hypoplastic ribs, wavy ribs and sternal irregularities, including fusions. The significance of these findings for humans is unknown.	on hERG (human ether-a-go-go related gene) tail currents, with an IC_{15} of 5.5 µM, which is comparable to the C_{max} (5.0 µM) for ivacaftor at the therapeutic dosage. However, no ivacaftor-induced QT prolongation was observed in a dog telemetry study at single doses of up to 60 mg/kg or in ECG measurements from repeat-dose studies of up to 1 year's duration at the 60 mg/kg/day dose level in dogs (C_{max} after 365 days = 36.2 to 47.6 µM). Ivacaftor produced a dose-related but transient increase in blood pressure parameters in dogs at single oral doses of up to 60 mg/kg. Ivacaftor did not cause reproductive system toxicity in male and female rats at 200 and 100 mg/kg/day, respectively. In females, dosages above this were associated with reductions in the overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in the oestrous cycle. In males, slight decreases of the seminal vesicle weights were observed. Ivacaftor was not teratogenic when orally dosed to pregnant rats and rabbits during the organogenesis stage of foetal development at doses resulting in exposures approximately 6 and 12 times the exposure in humans at the therapeutic dose, respectively. At maternally toxic doses in rats, ivacaftor produced reductions in foetal body weight and an increase in the incidence of cervical ribs, hypoplastic ribs, wavy ribs and sternal irregularities, including fusions. The significance of these findings for humans is unknown.	

Ivacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 100 mg/kg/day. Dosages above this produced 92% and 98% reductions of survival and lactation indices, respectively, as well as reductions in pup body weights. Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with dose levels of 10 mg/kg/day and higher (resulting in exposures 0.22 times the human exposure at the ~~maximum recommended human dose~~ MRHD based on systemic exposure of ivacaftor and its major metabolites; ~~exposures were obtained by non-compartmental analysis [NCA] of plasma concentrations of all patients in Study 5).~~ This finding has not been observed in foetuses derived from rat dams treated on gestation Day 7 to 17, in rat pups exposed to a certain extent through milk ingestion up to postnatal Day 20, in 7-week-old rats, or in 4- to 5-month-old dogs. The potential relevance of these findings in humans is unknown. Two-year studies in mice and rats to assess the carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in male and female mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 4-~~to~~ and 7-fold higher, respectively,~~higher~~ than the exposure measured in humans following ivacaftor therapy, and at least 1.2- and 2.4-fold higher, respectively, with regard to the summed AUCs for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in male and female rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately	Ivacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 100 mg/kg/day. Dosages above this produced 92% and 98% reductions of survival and lactation indices, respectively, as well as reductions in pup body weights. Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with dose levels of 10 mg/kg/day and higher (resulting in exposures 0.22 times the human exposure at the maximum recommended human dose based on systemic exposure of ivacaftor and its metabolites; exposures were obtained by non-compartmental analysis [NCA] of plasma concentrations of all patients in Study 5). This finding has not been observed in foetuses derived from rat dams treated on gestation Day 7 to 17, in rat pups exposed to a certain extent through milk ingestion up to postnatal Day 20, in 7-week-old rats, or in 4- to 5-month-old dogs. The potential relevance of these findings in humans is unknown. Two-year studies in mice and rats to assess the carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 4- to 7-fold,higher than the exposure measured in humans following ivacaftor therapy. Plasma exposures to ivacaftor in rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 17- to 31-fold,higher than the exposure measured in humans following ivacaftor therapy	

~~17~~16- ~~to~~ and ~~31~~29-fold higher, respectively,~~higher~~ than the exposure measured in humans following ivacaftor therapy, and 6- and 9-fold higher, respectively, with regard to the summed AUCs for ivacaftor and its major metabolites. Ivacaftor was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests.	Ivacaftor was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests.	

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

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