including monitoring of vital signs, liver function tests and observation of the clinical status of the patient.
"Should an overdose occur, go to the nearest hospital or contact any of the following Poison Control Centers:
HOSPITAL DE PEDIATRÍA RICARDO GUTIÉRREZ:
(011) 4962-6666/2247.
HOSPITAL ALEJANDRO POSADAS:
(011) 4654-6648/4658-7777
Alternatively, other Poison Control Centers"
As per international norms, IVACAR® adheres to the Risk Management Plan (PGR, Plan de Gestión de Riesgos).
PGR: It is a strategic safety program to minimize known potential risks of a product, while preserving its therapeutical benefits.
If you have questions, contact the Gador Pharmacovigilance Department ***by email to farmacovigilancia@gador.com o by phone at 0-800-220-2273 (CARE).***

HOW SUPPLIED: 60, 100, 500 and 1000 film-coated-tablet containers. Last two are for Hospital use only.

STORAGE AND HANDLING CONDITIONS
Keep in its original container at room temperature between 15ºC and 30°C.

"KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN"

"This medicinal product should be used only under medical prescription and cannot be repeated without a new medical prescription".

PATIENT INFORMATION LEAFLET

COMPOSITION
Each film-coated tablet of **IVACAR®** contains:
Ivacaftor.....150 mg
Sodium Lauryl sulfate, Hydroxypropylmethylcellulose Acetate Succinate, Sodium Croscarmellose, Microcrystalline Cellulose (Type 102), Lactose monohydrate CD30, colloidal anhydrous silica, Vegetable Magnesium Stearate, Indigotine aluminium lake, Opadry II 85F28751 White(Polyvinyl alcohol, Polyethylene glycol, Titanium dioxide and Talc), OpadryFX 62W28547 Silver (Sodium Carboxymethyl Cellulose, Maltodextrin, Dextrose Monohydrate, Mica-based Pearlescent Pigment (CI 77019 / CI 77891), Lecithin).

Read all the information concerning IVACAR® carefully before you start taking this medicine because it contains important information for you.
– Keep this leaflet because you may need to read it again.
– If you have any questions, ASK YOUR DOCTOR.
– This medicine has been prescribed only for you, and you must not pass it on to others, even if their symptoms are the same as yours because it may harm them.
– If you get any side effect, talk to your doctor, even if they are not listed in this leaflet.

1. What is IVACAR® and what is it used for?
IVACAR® contains the active ingredient ivacaftor. Ivacaftor acts at the level of the Cystic Fibrosis Transmembrane conductance Regulator (CFTR), a protein that forms a channel at the cell surface that allows particles such as chloride to move in and out of the cell. Due to mutations in the *CFTR* gene (see below), chloride movement is reduced in subjects with cystic fibrosis (CF). Ivacaftor helps certain abnormal CFTR proteins open more often to improve chloride movement in and out of the cell.
IVACAR® is indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one mutation in the CFTR gene that is sensitive to ivacaftor effect based on clinical data and/or in vitro assays.
Talk to your doctor to learn if you have an indicated mutation in the CF gene.

2. What do you need to know before you start taking IVACAR®?
Do not take IVACAR®
– If you are allergic to ivacaftor or to any of the other ingredients in this medicine.
Warnings and Precautions
Talk to your doctor if you have been told that you have liver or renal problems. Your doctor may need to adjust your dose of **IVACAR®**.
Abnormal liver results in blood tests have been observed in some people receiving **IVACAR®**. Tell your doctor right away if you have any of these symptoms, which may be a sign of liver problems:
• Pain or discomfort in the upper right abdominal area
• Yellowing of the skin or the white part of the eyes
• Loss of appetite
• Nausea or vomiting
• Dark urine
Your doctor will order some blood tests to check your liver functions before and during **IVACAR®** treatment, particularly during the first year and especially if you have had high liver enzymes in the past.
An abnormality of the eye lens (cataract) without any effect on vision has been noted in some children and adolescents treated with **IVACAR®**.
Your doctor may perform some eye examinations prior to and during treatment with **IVACAR®**.
IVACAR® is not recommended in patients who have undergone an organ transplantation
Children
The film-coated tablet formulation is not appropriate for children under 6 years of age.
Use of **IVACAR®** tablets is not appropriate for children under 6 years of age.
Ivacaftor might not work in 6- to 11-year-old CF patients who have an *R117H* mutation.
IVACAR® with other medicines
IVACAR® may interact with other medicines. Tell your doctor if you are taking or have recently taken or are considering taking any other medicines, including medicines obtained without a prescription, such as herbal supplements.
Some medicines can affect how **IVACAR®**, works, or make side effects more likely. **IVACAR®** can also affect how other medicines work.
Tell your doctor if you are taking any of the following medicines:
• Ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole, antifungal medicines used for the treatment of fungal infections.
• Telithromycin, clarithromycin, erythromycin, rifampicin, rifabutin, antibiotic medicines used for the treatment of bacterial infections.
• Phenobarbital, carbamazepine, phenytoin, anticonvulsant medicines used for the treatment of epileptic seizures.
• Herbal medicines such as St. John's wort (Hypericum perforatum).
• Midazolam, alprazolam, diazepam, triazolam, benzodiazepines used for the treatment of anxiety, insomnia, agitation, etc.
• Cyclosporine, tacrolimus, immunosuppressants used after an organ transplantation.
• Digoxin, cardiac glycosides used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation.
• Warfarin, anticoagulants used to prevent blood clots from forming or growing larger in blood and blood vessels.
• Medicinal products for diabetes, such as glimepiride and glipizide, used to reduce blood sugar levels.
Tell your doctor if you are taking any of these medicines. Your doctor may decide to adjust your dose or that you need extra checkups.
IVACAR® with food and drinks
Avoid food or drinks containing grapefruit or Seville oranges during treatment with **IVACAR®** as they may increase the amount of ivacaftor in your body.
Pregnancy and breast-feeding
If you are pregnant or breast-feeding, you think you may be pregnant or are planning to get pregnant, ask your doctor for advice before taking this medicine. If possible, it might be preferable to avoid **IVACAR®** use during pregnancy, and your doctor will help you decide what is best for you and your child.
It is unknown whether ivacaftor is excreted into human milk.
If you plan to breast-feed, tell your doctor before taking IVACAR®. Your doctor will decide whether to recommend that you stop breast-feeding or stop ivacaftor therapy. Your doctor will take into account the benefit of breast-feeding for the child and the benefit of therapy for you.
Driving and using machines
IVACAR® can make you feel dizzy. You should not drive or operate machines unless you are sure it does not affect you.

3. How to take IVACAR®?
Always take this medicine exactly as your doctor has told you. If in doubt, check again with your doctor. Your doctor will tell you how much **IVACAR®** to take
How to take this medicine
IVACAR® should be taken orally with food that contains fat. Recommended foods for patients with cystic fibrosis within standard nutritional indications have an appropriate fat content. Examples of fat-containing foods include those prepared with butter or oil, those containing eggs, cheeses, nuts, whole milk, yogurt, chocolate or meats. Taking **IVACAR®**, with fat-containing food is important to get the right levels of medicine in your body.
Swallow the tablet whole. Do not chew, break or dissolve the tablets before swallowing.
If you forgot to take IVACAR®
If less than 6 hours have passed since the time you missed the dose, take the missed dose. Otherwise, wait until your next scheduled dose as you normally would. Do not take a double dose to make up for a missed dose.
If you stop taking IVACAR®
Take **IVACAR®** for as long as your doctor indicates. Do not stop therapy unless your doctor tells you to do so. If you discontinue therapy, tell your doctor. If you have any further questions on the use of this medicine, ask your doctor.
If you take more IVACAR® than you should
You may experience side effects, including those mentioned in item 4 below. If so, contact your doctor.
"Should an overdose occur, go to the nearest hospital or contact any of the following Poison Control Centers:
HOSPITAL DE PEDIATRÍA RICARDO GUTIÉRREZ:
(011) 4962-6666/2247.
HOSPITAL ALEJANDRO POSADAS:
(011) 4654-6648/4658-7777
Alternatively, other Poison Control Centers".

4. What are the possible side effects of IVACAR®?
Like all medicines, **IVACAR®** can cause side effects, although not everybody gets them.
Most frequent and serious side effects include stomach (abdominal) pain, increased liver enzymes in the blood and hypoglycemia. Contact your doctor right away if you get any of these side effects.
Other side effects according to their frequency are:
Very common (may affect more than 1 in 10 people)
• Upper respiratory tract infection (common cold), which includes sore throat and nasal congestion
• Headache
• Dizziness
• Diarrhea
• Skin Rash
• Changes in the type of bacteria in mucus
Common (may affect up to 1 in 10 people)
• Ear pain, ear discomfort
• Ringing in the ears
• Redness inside the ear
• Inner ear disorder (feeling dizzy or spinning)
• Sinus congestion
• Runny nose
• Nausea
• Redness in the throat
• Joint pain
• Breast mass
• Joint pain
• Muscle pains
• Pleuritic pain
• Wheezing
• Acne
• Increased blood glucose
Uncommon (may affect up to 1 in 100 people)
• Ear congestion
• Breast inflammation
• Enlargement of breasts
• Nipple changes or pain
Additional side effects in children and adolescents
Side effects observed in children and adolescents are similar to those observed in adults. However, increased liver enzymes in the blood are more frequently seen in young children.
Tell your doctor if you have any side effect that bothers you or that does not go away, even if it is not listed in this leaflet. These are not all the possible side effects of IVACAR®. For more information, ask your doctor.
If you experience any type of side effect, tell your doctor, even if it is not listed in this leaflet. You may also contact GADOR S.A Pharmacovigilance Department, phone +54 (11) 4858-9000 (ext. 229) or by mail to farmacovigilancia@gador.com.

5. How should you store IVACAR®?
• Keep **IVACAR®** in its original container at room temperature between 15ºC and 30°C.
• Do not use **IVACAR®** after the expiry date shown on the container.

"KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN"

HOW SUPPLIED: 60 film-coated-tablet containers.

As per international norms, IVACAR® adheres to the Risk Management Plan (PGR, Plan de Gestión de Riesgos).
PGR: It is a strategic safety program to minimize known potential risks of a product, while preserving its therapeutical benefits.
For queries, contact Gador Pharmacovigilance Department by email to farmacovigilancia@gador.com o by phone at 0-800-220-2273 (CARE).

"This medicine has been prescribed only for your present medical condition. Do not recommend it to other people".

THIS MEDICINAL PRODUCT SHOULD BE USED ONLY UNDER MEDICAL PRESCRIPTION AND SURVEILLANCE AND CANNOT BE REPEATED WITHOUT A NEW MEDICAL PRESCRIPTION.

Gador

Get more information visiting our website www.gador.com.ar/productos or request through email to info@gador.com

Manufacturer and MAH GADOR S.A.
Darwin 429 - C1414CUI, C.A.B.A. Argentina - Phone: +54 11 4858-9000 Technical Director: Jorge N. Naquit - Pharmacist and Lic. in Pharmaceutical Sciences
Medicinal Product authorized by the National Ministry of Health and Sustainable Development. Certificate Nº 58.757
Date of last revision:03 / 2020
GXXXXXXXXX-XX

Recyclable Materials

Gador

IVACAR®
IVACAFTOR 150 mg

Filed Rx only medicine
Made in Argentina

Film-coated Tablets

COMPOSITION
Each film-coated tablet of **IVACAR®** contains:
Ivacaftor.....150 mg
Sodium Lauryl sulfate, Hydroxypropylmethylcellulose Acetate Succinate, Sodium Croscarmellose, Microcrystalline Cellulose (Type 102), Lactose monohydrate CD30, colloidal anhydrous silica, Vegetable Magnesium Stearate, Indigotine aluminium lake, Opadry II 85F28751 White(Polyvinyl alcohol, Polyethylene glycol, Titanium dioxide and Talc), OpadryFX 62W28547 Silver (Sodium Carboxymethyl Cellulose, Maltodextrin, Dextrose Monohydrate, Mica-based Pearlescent Pigment (CI 77019 / CI 77891), Lecithin).

THERAPEUTIC ACTION
Pharmacotherapeutic group: Other respiratory system products.
ATC Code: R07AX02
INDICATIONS
IVACAR® is indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing ≥25 kg who have one mutation in the Cystic Fibrosis Transmembrane conductance Regulator (*CFTR*) gene that is sensitive to ivacaftor effect based on clinical data and/or*n vitro* assays described in Mechanism of Action.
Approved indications are subject to verification in confirmatory trials.

PHARMACOLOGICAL ACTION
Mechanism of Action
Ivacaftor is a potentiator of the CFTR protein. CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. *In vitro*, ivacaftor increases CFTR channel gating to enhance chloride transport in specified gating mutations (see **Table 1**).
The general level of chloride transport of ivacaftor-mediated CFTR depends on the quantity of CFTR protein on the cell surface and the response showed by a particular CFTR protein with mutation to the ivacaftor potentiation.
Patients must have at least one mutation of CFTR responsive to ivacaftor for it to be indicated.

Table 1 shows mutations responsive to ivacaftor according to 1) a positive clinical response and/or 2) *in vitro* data in Fisher Rat Thyroid (FRT) cell line indicating that ivacaftor increases chloride transport to at least 10% above reference values (% of normal).

Table 1: List of CFTR gene mutations producing CFTR protein and responsive to ivacaftor

E56K	*G178R*	*S549R*	*S977F*	*F1074L*	*2789+5G→A*
P67L	*E193K*	*G551D*	*F1052V*	*D1152H*	*3272-26A→G*
R74W	*L206W*	*G551S*	*K1060T*	*G1244E*	*3849+10kbC→T*
D110E	*R347H*	*D579G*	*A1067T*	*S1251N*	
D110H	*R352Q*	*711+3A→G*	*G1069R*	*S1255P*	
R117C	*A455E*	*E831X*	*R1070Q*	*D1270N*	
R117H	*S549N*	*S945L*	*R1070W*	*G13490D*	

The *G970R* mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface that can be potentiated by ivacaftor. Ivacaftor also increased chloride transport in cultured Human Bronchial Epithelial (HBE) cells derived from CF patients who had *F508del* on one *CFTR* allele and either *G551D* or *R117H-5T* on the second *CFTR* allele.

PHARMACOKINETICS
The pharmacokinetics (PK) of ivacaftor is similar between healthy adult volunteers and CF patients.
After oral administration of a single 150 mg dose to healthy volunteers in a fed state, peak plasma concentrations (T_{max}) were reached at approximate 4 hours, and the mean (±SD) for AUC and C_{max} were 10,600 (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.
Absorption
Following multiple oral doses, 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, **IVACAR®** should be administered with fat-containing food. The median (range) T_{max} is approximately 4.0 (3.0; 6.0) hours in the fed state.
Distribution
Ivacaftor is approximately 99% bound to plasma proteins, mainly 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 to healthy volunteers in the fed state, the mean (±SD) apparent volume of distribution was 353 (122) L.
Biotransformation
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.
The effect of the activity potentially reduced of CYP3A4 in patients who have the CYP3A4*22 variant on ivacaftor exposure is unknown.
Elimination
Following oral administration of ivacaftor, most of the drug (87.8%) was eliminated in the feces after metabolic conversion. The 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 drug. The apparent terminal half-life was approximately 12 hours following a single dose in the fed state. The mean apparent clearance (CL/F)

of ivacaftor was similar for healthy subjects and CF patients. The CL/F (±SD) for a single 150 mg dose was 17.3 (8.4) L/hr in healthy subjects.

Dose/time proportionality

The pharmacokinetics of ivacaftor is generally linear with respect to time or dose ranging from 25 mg to 250 mg.

Special Populations

Hepatic Impairment

Following a single dose of 150 mg of ivacaftor, adult subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had a similar ivacaftor C_{max} (mean [±SD] of 735 [331] ng/mL) but an approximately two-fold increase in ivacaftor AUC0-∞ (mean [±SD) of 16 800 [6140] ng*hr/mL) compared to healthy subjects matched for demographics. Simulations to predict the steady-state exposure of ivacaftor showed that by reducing dosage from 150 mg every 12 hours to 150 mg once daily, adults with moderate hepatic impairment would have steady-state C_{min} values similar to those obtained with a dose of 150 mg every 12 hours in adults without hepatic impairment. Therefore, a reduced 150 mg dose once daily is recommended for patients with moderate hepatic impairment. 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 AUC0-∞ is expected to be less than two-fold. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment.

No studies have been conducted in patients with severe hepatic impairment (Child Pugh Class C, score 10 to 15) but exposure is expected to be higher than that observed in patients with moderate hepatic impairment. Therefore, the use of ivacaftor in patients with severe hepatic impairment is not recommended unless the benefits outweigh the risks. In such cases, the initial dose should be 150 mg every other day. Dosing intervals should be adjusted according to clinical response and tolerability (see ***DOSAGE AND ADMINISTRATION and PRECAUTIONS***).

Renal Impairment

Pharmacokinetic studies have not been conducted 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 drug (less than 0.01% following a single oral dose of 500 mg). Therefore, no dose adjustments are recommended in patients with mild or 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 ***PRECAUTIONS and PHARMACOKINETICS***).

Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). For patients with moderate hepatic impairment (Child-Pugh Class B), a reduced dose of 150 mg once daily is recommended. There is no experience on the use of **IVACAR®** in patients with severe hepatic impairment and, therefore, its use is 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 adjusted according to clinical response and tolerability (see ***PRECAUTIONS AND PHARMACOKINETICS***).

Concomitant use of CYP3A inhibitors

When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole; telithromycin and clarithromycin), the **IVACAR®** dose should be reduced to 150 mg twice a week (see ***PRECAUTIONS***).

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the **IVACAR®** dose should be reduced to 150 mg once daily (see ***PRECAUTIONS***).

Pediatric Population

An appropriate dose for children aged less than 6 years and weighing less than 25 kg cannot be obtained with the film-coated tablet formulation.

The film-coated formulation is not appropriate for children less than 6 years old.

The efficacy of **IVACAR®** in children aged less than 18 years with an *R117H* mutation in the *CFTR* gene has not been established (see ***PRECAUTIONS).***

Elderly Patients

Though very limited data are available for elderly patients with an *R117H* mutation in the *CFTR* gene treated with ivacaftor, no dose adjustment is considered necessary unless moderate hepatic impairment exists. Caution is recommended for patients with severe renal impairment or end-stage renal disease.

Table 2. Mean (SD) ivacaftor exposure by age group

Age Group	Dose	C_{max} ss (ng/mL)	$AUC_{T, ss}$ (ng.h/mL)
6 to 11 years old (≥25 kg)	150 mg q12h	958 (546)	15300 (7340)
12 to 17 years old	150 mg q12h	564 (242)	9240 (3420)
Adults (≥18 years old)	150 mg q12h	701 (317)	10700 (4100)

Gender

The effect of gender on pharmacokinetics was evaluated. No dose adjustments are necessary based on gender.

Race

According to population PK analysis, race had no clinically significant effect on the ivacaftor PK in white and non-white patients.

Elderly patients

Clinical trials of ivacaftor did not include enough number of patients 65 years of age and older to determine whether PK parameters are similar to those of younger adult patients.

DOSAGE AND ADMINISTRATION

IVACAR® should only be prescribed by physicians with experience in the treatment of cystic fibrosis. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed before starting treatment to confirm the presence of one of the previously mentioned *CFTR* gene (see ***PHARMACOLOGICAL ACTION***). The phase of the poly-T variant identified with the *R117H* mutation should be determined in accordance with local clinical recommendations.

Dosage

Adults, adolescents, and children aged 6 years and older and weighing ≥ 25 kg

The recommended **IVACAR®** dose is 150 mg orally every 12 hours (300 mg total daily dose) with fat-containing food.

Recommended foods for patients with CF within standard nutritional indications contain an appropriate fat content. Examples of appropriate fat-containing foods include those prepared with butter or oils, those containing eggs, cheeses, nuts, whole milk, yogurt or meats.

Food or drinks containing grapefruit or Seville oranges should be avoided during treatment with **IVACAR®** (see ***PRECAUTIONS***).

Patients should be instructed to swallow the tablets whole (i.e., tablets should not be chewed, broken or dissolved before swallowing).

Missed Doses

If a dose is missed within 6 hours of the time it is usually taken, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. If more than 6 hours have passed since the time the dose is usually taken, the patient should be told to wait until the next scheduled dose.

Specific Populations

Renal Impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended during treatment with **IVACAR®** in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see ***PRECAUTIONS and PHARMACOKINETICS***).

Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). For patients with moderate hepatic impairment (Child-Pugh Class B), a reduced dose of 150 mg once daily is recommended. There is no experience on the use of **IVACAR®** in patients with severe hepatic impairment and, therefore, its use is 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 adjusted according to clinical response and tolerability (see ***PRECAUTIONS AND PHARMACOKINETICS***).

Concomitant use of CYP3A inhibitors

When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole; telithromycin and clarithromycin), the **IVACAR®** dose should be reduced to 150 mg twice a week (see ***PRECAUTIONS***).

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the **IVACAR®** dose should be reduced to 150 mg once daily (see ***PRECAUTIONS***).

Pediatric Population

An appropriate dose for children aged less than 6 years and weighing less than 25 kg cannot be obtained with the film-coated tablet formulation.

The film-coated formulation is not appropriate for children less than 6 years old.

The efficacy of **IVACAR®** in children aged less than 18 years with an *R117H* mutation in the *CFTR* gene has not been established (see ***PRECAUTIONS).***

Elderly Patients

Though very limited data are available for elderly patients with an *R117H* mutation in the *CFTR* gene treated with ivacaftor, no dose adjustment is considered necessary unless moderate hepatic impairment exists. Caution is recommended for patients with severe renal impairment or end-stage renal disease.

Administration

IVACAR® should be administered orally. It should be taken with fat-containing food. Patients should be instructed to swallow the tablets whole (i.e. tablets should not be chewed, broken or dissolved before swallowing).

Food or drinks containing grapefruit or Seville oranges should be avoided during treatment with **IVACAR®**.

CONTRAINDICATIONS

IVACAR® is contraindicated in subjects with hypersensitivity to the active substance or to any of the inactive ingredients (see ***COMPOSITION***).

WARNINGS AND PRECAUTIONS

Warnings

There are only limited data of patients who have the *G551D* mutation in the CFTR gene with less than 40% predicted FEV_1 (Forced Expiratory Volume during the first second).

Clinical efficacy in patients with the *G970R* mutation in the CFTR gene has not been established.

No studies have been conducted with ivacaftor in other CF patient populations. Therefore, it is not recommended for use in these patients.

Efficacy in patients aged 6 to 11 years with CF who have an *R117H* mutation has not been demonstrated.

There is evidence of a less positive effect in patients with an *R117H-7T* mutation associated with less severe disease. Whenever possible, the phase of the poly-T variant identified in the R117H mutation should be determined as this information may be useful when considering treating patients with an *R117H* mutation (see ***DOSAGE AND ADMINISTRATION).***

Precautions

Effect on Liver Function Tests

Moderate transaminase (alanine transaminase [ALT] or aspartate transaminase [AST]) elevations are common in subjects with CF. Liver function tests are recommended for all patients prior to initiating ivacaftor therapy, every 3 months during the first year of treatment and annually thereafter. For all patients with a history of increased transaminases, more frequent monitoring of liver function tests should be considered.

Patients who develop transaminases elevations should be closely followed until the abnormalities resolve. Dosing should be discontinued in patients with ALT or AST >5 x ULN (Upper Limit of Normal) or ALT or AST >3 x ULN with bilirubin >2 x ULN. Once transaminase elevations have been resolved, the benefits and risks of resuming treatment with **IVACAR®** should be outweighed.

Hepatic Impairment

Use of ivacaftor is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks of overexposure. In such cases, the starting dose should be 150 mg every other day (see ***PHARMACOKINETICS and DOSAGE AND ADMINISTRATION***).

Renal Impairment

Caution is recommended while using ivacaftor in patients with severe renal impairment or end-stage renal disease (see ***PHARMACOKINETICS and DOSAGE AND ADMINISTRATION***).

Patients after Organ Transplantation

Ivacaftor has not been studied in CF patients who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended (see ***INTERACTIONS*** with cyclosporine, tacrolimus).

Cataracts

Cases of non-congenital cataracts/lens opacity without impact on vision have been reported in pediatric patients treated with ivacaftor. Although other risk factors were present in some cases (such as corticosteroid use or exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with **IVACAR®**.

Drug Interactions

Ivacaftor is a substrate of CYP3A4 and CYP3A5. It is a weak inhibitor of CYP3A and P-gp and a potential inhibitor of CYP2C9.

Medicinal products that inhibit or induce CYP3A activity may affect ivacaftor pharmacokinetics:

Ivacaftor exposure may diminish when co-administered with CYP3A inducers, and may lead to a potential loss of ivacaftor efficacy. Therefore, co-administration with strong CYP3A inducers is not recommended. Ivacaftor dose should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see ***DOSAGE AND ADMINISTRATION***).

In vitro assays showed ivacaftor is not a substrate of OATP1B1, OATP1B3 or P-gp. If ivacaftor and/or its metabolites are substrates of BCRP is unknown.

Medicinal Products Affecting the Pharmacokinetics of Ivacaftor

CYP3A Inhibitors

Ivacaftor is a sensitive CYP3A substrate. Co-administration with ketoconazole, a strong CYP3A inhibitor, significantly increased ivacaftor exposure, measured as area under the curve (AUC), by 8.5-fold and increased M1 metabolite to a lesser extent than ivacaftor. It is recommended to reduce ivacaftor dose to 150 mg twice weekly if co-administered with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin.

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased exposure of ivacaftor by 3-fold and that of its M1 metabolite, though to a lesser extent than ivacaftor. Therefore, it is recommended to reduce ivacaftor dose to 150 mg once daily in patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

Co-administration of ivacaftor with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ivacaftor. Therefore, food or drinks containing grapefruit or Seville oranges should be avoided during treatment with ivacaftor.

CYP3A Inducers

Co-administration of ivacaftor with rifampicin, a strong CYP3A inducer, significantly decreased (89%) ivacaftor exposure (AUC) and decreased M1 exposure, though to a lesser extent, which may result in **IVACAR®** therapeutic efficacy being reduced. Therefore, co-administration with strong CYP3A inducers, such as rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's wort (*Hypericum perforatum*) is not recommended.

Concomitant use with weak to moderate CYP3A inducers (e.g. high dose prednisone, dexamethasone) may reduce exposure of ivacaftor. No ivacaftor dose adjustment is recommended. When co-administering ivacaftor with moderate CYP3A inducers, patients should be closely monitored for reduced ivacaftor efficacy.

Ciprofloxacin

Co-administration of ivacaftor with ciprofloxacin did not affect the exposure of ivacaftor. Therefore, no dose adjustment is required during concomitant administration of **IVACAR®** with ciprofloxacin.

Effect of Ivacaftor on Other Medicinal Products

Ivacaftor administration may increase systemic exposure of medicinal products that are sensitive CYP3A, P-gp and/or CYP2C9 substrates, which may increase or prolong its therapeutical effect and adverse reactions.

CYP2C9 Substrates

Ivacaftor may inhibit CYP2C9. Therefore, monitoring the International Normalized Ratio (INR) during co-administration of **IVACAR®** with warfarin is recommended. The exposure of other medicinal products may be increased, including glimepiride and glipizide; caution is recommended when administering these medicinal products.

Digoxin and other P-gp substrates

Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of **IVACAR®** may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Therefore, caution and appropriate monitoring are recommended when co-administering with digoxin or other P-gp substrates with a narrow therapeutical index such as cyclosporine, everolimus, sirolimus or tacrolimus

CYP34 substrates

Co-administration with midazolam (oral), a sensitive CYP3A substrate, increased midazolam exposure by 1.5-fold, which is consistent with weak inhibition of CYP3A by ivacaftor. No dose adjustment of CYP3A substrates, such as midazolam, alprazolam, diazepam or triazolam, when co-administering with ivacaftor is necessary. **IVACAR®** must be used with caution and patients should be monitored for undesired benzodiazepine-related side effects.

Further Recommendations

Ivacaftor has been studied with an estrogen/progesterone **oral contraceptive** and was found to have no significant effect on the exposure of the oral contraceptive. Ivacaftor is not expected to affect the efficacy of oral contraceptives. Therefore, no dose adjustment of oral contraceptives is necessary.

Ivacaftor has been studied with the CYP2D6 substrate desipramine. No significant effect on desipramine exposure was found. Therefore, no dose adjustment of CYP2D6 substrates such as desipramine is necessary.

Ivacaftor has been studied with the CYP2C8 substrate rosiglitazone. No significant effect on rosiglitazone exposure was found. Therefore, no dose adjustment of CYP2C8 substrates such as rosiglitazone is necessary.

Interaction studies have been conducted only in adult patients.

Pregnancy, Lactation and Fertility

Pregnancy

No adequate and well-controlled studies have been conducted with ivacaftor in pregnant women. Ivacaftor was not teratogenic when dosed orally to pregnant rats and rabbits during the organogenesis stage of fetal development at doses that produced exposures of up to approximately 5- (in rats)) and 11- (in rabbits) fold the exposure at the maximum recommended human dose, (see ***Non-Clinical Safety Data***). Animal reproduction studies are not always predictive of human response. Preferably, as a precautionary measure, use of **IVACAR®** should be avoided during pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

Breast-feeding

It is unknown whether ivacaftor and/or its metabolites are excreted into human milk. Available pharmacokinetic data in animals have shown excretion of ivacaftor into the milk of lactating female rats. The risk to the newborns/infants cannot be excluded, therefore, ivacaftor may be used during breast-feeding only if potential benefits outweigh potential risks.

Fertility

Human fertility data of ivacaftor effect are not available. Ivacaftor affected fertility in rats.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (yielding exposures approximately 8- and 5- fold, respectively, the maximum recommended human dose based on summed AUCs of ivacaftor and its major metabolites) when dams were dosed prior to and during early pregnancy (see ***Non-clinical Safety Data***). No effects on fertility and reproductive performance indices were observed in male and female rats at ≤100 mg/kg/day (yielding exposures approximately 6 and 3 times, respectively, the maximum recommended human dose based on summed AUCs of ivacaftor and its major metabolites).

Pediatric Use

Ivacaftor is indicated for CF treatment in patients ≥ 6 years of age having one CFTR gene mutation responsive to ivacaftor potentiation based on clinical data and/or in vitro assays (see ***Pharmacological Action***).

Placebo-controlled clinical trials demonstrated efficacy and safety on the following CF patients:

- 6 to 17 years of age with one *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H* mutation in the CFTR gene.
- 12 to 17 years of age who are heterozygous for the *F508del* mutation and have second mutation predicted to be responsive to Ivacaftor.

The film-coated tablet formulation is not appropriate for children <6 years of age.

Geriatric use

CF is mainly a disease of children and young adults. Clinical trials of ivacaftor did not include sufficient number of patients 65 years of age and older to determine whether they respond differently from younger patients.

Effects on the ability to drive and use machines

Ivacaftor may cause dizziness (see ***ADVERSE REACTIONS***), and, therefore, patients experiencing dizziness should be advised not to drive or use machines until symptoms remittance.

Non-clinical Safety Data

Data from non-clinical studies do not show special risks for humans based on pharmacology conventional studies of safety, toxicity and repeated doses, genotoxicity and carcinogenic potential.

Effects were only observed in non-clinical studies at exposures considered sufficiently higher than the maximum human exposure, indicating negligible relevance for the clinical use.

Ivacaftor produced concentration-dependent inhibition of hERG (human ether-à-go-go related gene) tail currents, with an IC_{10} of 5.5 µM, which is comparable to the C_{max} (5.0 µM) of ivacaftor at the therapeutic doses. However, no ivacaftor-related QT interval 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 in dogs of up to 1 year duration at 60 mg/kg/day (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. Dosages above 100 mg/kg/day in females were associated to decreases in overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in estrous cycle. In males, slight weight decreases of the seminal vesicles were observed.

Ivacaftor was not teratogenic when dosed orally to pregnant rats and rabbits during the organogenesis stage of fetal development at doses resulting in exposures of up to approximately 5 (based on summed AUCs of ivacaftor and its major metabolites) and 11 (based on ivacaftor AUC) times the exposure at the maximum recommended human dose, respectively. At maternally toxic doses in rats, ivacaftor produced reductions in fetal body weight, 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 resulted in 92% and 98% reduction in survival and lactation indices, respectively, as well as decreases in pup body weights.

Cataracts were observed in juvenile rats dosed from post-natal day 7 through 35 with dose levels of 10 mg/kg/day and higher (resulting in 0.22 times the maximum recommended human dose based on systemic exposure of ivacaftor and its major metabolites). This finding has not been observed in fetuses from rat dams treated on gestation day 7 to 17, in rat pups exposed to a certain extent through breast milk up to post-natal 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 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 7-fold higher, respectively, than the plasma levels measured in humans following ivacaftor therapy, and at least 1.2- to 2.4-fold higher, respectively, in regards to the summed AUCs of 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 16- to 29-fold higher, respectively, than the exposure mea

sured in humans following ivacaftor therapy, and 6- to 9-fold higher, respectively, in regards to the summed AUCs of ivacaftor and its major metabolites.

Ivacaftor was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests.

ADVERSE REACTIONS

Summary of Safety Profile

Most frequent serious adverse reactions observed in clinical trials in patients who received ivacaftor included abdominal pain, transaminases elevations and hypoglycemia (see ***WARNINGS***).

Table of Adverse Reactions

Table 3 shows the adverse reactions observed with ivacaftor. 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), unknown frequency (could not be estimated based on the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions in ivacaftor-treated patients aged 6 years and older

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Nasopharyngitis
	Very common	Upper respiratory tract infection
	Common	Rhinitis
Nervous system disorders	Very common	Headache
	Very common	Dizziness
Ear and labyrinth disorders	Common	Ear discomfort
	Common	Ear pain
	Common	Tinnitus
	Common	Tympanic membrane hyperemia
	Uncommon	Ear congestion
	Common	Vestibular disorder
Respiratory, thoracic and mediastinal disorders	Very common	Nasal congestion
	Very common	Oropharyngeal pain
	Common	Pharyngeal erythema
	Common	Sinus congestion
	Common	Pleuritic pain
	Common	Wheezing
Gastrointestinal disorders	Very common	Abdominal pain
	Very common	Diarrhea
	Common	Nausea*
Hepatobiliary disorders	Very common	Transaminase elevations
Skin and subcutaneous tissue disorders	Very common	Exanthema
	Common	Acné
Reproductive system and breast disorders	Uncommon	Breast inflammation
	Common	Breast mass
	Uncommon	Gynaecomastia
	Uncommon	Nipple disorder
	Uncommon	Nipple pain
Musculoskeletal and connective tissue disorders	Common	Arthralgia
	Common	Myalgia
	Common	Musculoskeletal chest pain
Complementary Investigations	Very common	Bacteria in sputum
	Common	Increased glycemia
	Unknown frequency	Hypoglycemia

*Frequency and adverse reaction notified only in combined clinical studies with tezacaftor/ivacaftor

Description of Selected Adverse Reactions

Exanthema:

Data collected indicate that most of these events were non-serious and that most of these patients did not discontinue therapy because of exanthema.

Ear and labyrinth disorders

The incidence of ear and labyrinth disorders was 9.2% in ivacaftor-treated patients. Most events were described as mild to moderate in severity; only one event of ear pain was described as severe; none were serious and no patients discontinued treatment because of ear and labyrinth disorders.

Nervous system disorders

Headache:

The incidence of headache was 23.9% in ivacaftor-treated patients. Data from all clinical trials and post-marketing data indicate that most of these events were non-serious and most of these patients did not discontinue therapy because of headaches.

Dizziness

The incidence of dizziness was 9.2% in ivacaftor-treated patients. Data from all clinical trials and post-marketing data indicate that most of these events were non-serious and most of these patients did not discontinue therapy because of dizziness.

Upper respiratory tract reactions

The incidence of upper respiratory tract reactions (upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) was 63.3% in ivacaftor-treated patients. Most events were described as mild to moderate in severity, one event of upper respiratory tract infection and one event of nasal congestion were considered to be severe, none were serious, and no patients discontinued treatment because of upper respiratory tract reactions.

Hepatobiliary disorders

Transaminases Elevation

The incidence of maximum transaminases (ALT or AST) levels >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 increased total bilirubin >1.5 x ULN. In ivacaftor-treated patients, most transaminase elevations of up to 5 x ULN resolved without discontinuing treatment. Ivacaftor dosing was interrupted in most patients with transaminase elevations >5 x ULN. In all instances where dosing was interrupted due to elevated transaminases and was subsequently resumed, ivacaftor dosing was able to be resumed successfully (see ***PRECAUTIONS***).

Pediatric population

Typically, safety profile is consistent between children and adolescents and is also consistent with adult patients.

In children from 6 to less than 12 years of age, the incidence of patients presenting aminotransferases elevation (ALAT or ASAT) >3 times the ULN was 15.0% (6/40) in ivacaftor-treated patients and 14.6% (6/41) in patients on placebo. Only one ivacaftor-treated patient (2.5%) in this age group presented an increase of ALAT and ASAT >8 x ULN. In general, the highest increases in the liver function tests (ALAT or ASAT) were larger in pediatric patients than in older patients. In almost every case where dosing was interrupted due to aminotransferases elevation and subsequently resumed, ivacaftor dosing was able to be resumed successfully. Cases indicative of positive re-exposure were observed.

Reporting of Suspected Adverse Reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Pharmacovigilance System using the following link: http://sistemas.anmat.gov.ar/aplicaciones_net/fvg_eventos_adversos_nuevo/index.htlm and/or GADOR S.A. Pharmacovigilance Department, by email to farmacovigilancia@gador.com or by phone at 0800-220-2273.

OVERDOSE

No specific antidote is available for overdose with Ivacaftor. Treatment of overdose consists of general supportive measures