Your doctor is the best resource for medical advice and information. The health information contained herein is provided for educational / awareness purposes only and is not intended to replace discussions with a medical practitioner and/or medical advice or be construed as a promotional information.

Package Leaflet: Information for the user
ISAVUCONAZOLE
100 mg Capsule &
200 mg Injection
CRESEMBA®

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CRESEMBA (Isavuconazole) is and what it is used for
2. What you need to know before you take CRESEMBA (Isavuconazole)
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1. What CRESEMBA (Isavuconazole) is and what it is used for

What CRESEMBA (Isavuconazole) is
Cresemba is an anti-fungal medicine that contains the active substance isavuconazole.

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How CRESEMBA (Isavuconazole) works
CRESEMBA (Isavuconazole) works by killing or stopping the growth of the fungus, which causes the infection.

What CRESEMBA (Isavuconazole) is used for
CRESEMBA (Isavuconazole) is used for patients 18 years of age and older, for the treatment of invasive aspergillosis and invasive mucormycosis.

2. What you need to know before you take CRESEMBA (Isavuconazole)

Do not take CRESEMBA (Isavuconazole)

If you are allergic to CRESEMBA (Isavuconazole) or any of the other ingredients of this medicine (listed in section 6).

- **If you have a heart beat problem called 'familial short QT syndrome'**,
- **If you are using any of the following medicines:**
    - Ketoconazole, used for fungal infections,
    - High doses of ritonavir (more than 200 mg every 12 hours), used for HIV,
    - Rifampicin, rifabutin, used for tuberculosis,
    - Carbamazepine, used for epilepsy,
    - Barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
    - Phenytoin, used for epilepsy,
    - St John's wort, a herbal medicine used for depression,
    - Efavirenz, etravirine, used for HIV,
    - Nafcillin, used for bacterial infections.

  In particular, do not take these medicines and tell your doctor if you are taking any of the above mentioned medicines.

Warnings and precautions

Talk to your doctor, before using CRESEMBA (Isavuconazole):
- If you have had an allergic reaction to other 'azole' anti-fungal treatments in the past, such as ketoconazole, fluconazole, itraconazole, voriconazole or posaconazole,
- If you are suffering from severe liver disease. Your doctor should monitor you for possible side effects.

Look out for side effects

Stop using CRESEMBA (Isavuconazole) and tell your doctor straight away if you notice any of the following side effects:
- Sudden wheezing, difficulty breathing, swelling of the face, lips, mouth or tongue, severe itching, sweating, dizziness or fainting, fast heartbeat or pounding in the chest – these may be signs of a severe allergic reaction (anaphylaxis).

Problems while having CRESEMBA (Isavuconazole) as drip into a vein
Tell your doctor straight away if you notice any of the following side effects:
- Low blood pressure, feel short of breath, nausea, dizziness, headache, tingling – your doctor may decide to stop the infusion.

Changes in your liver function
CRESEMBA (Isavuconazole) can sometimes affect your liver function. Your doctor may carry out blood tests while you are taking this medicine.

Skin problems
Tell your doctor straight away if you get severe blistering of the skin, mouth, eyes or genitals.

Children and adolescents
CRESEMBA (Isavuconazole) should not be used in children or adolescents younger than 18 years because there is no information on use in this age group.

Other medicines and CRESEMBA (Isavuconazole)
Tell your doctor if you are using, have recently used or might use any other medicines. Some medicines may affect the way CRESEMBA (Isavuconazole) works or CRESEMBA (Isavuconazole) may affect the way they work, if they are taken at the same time.

Unless your doctor tells you otherwise, do not take this medicine and tell your doctor if you are taking any of the following medicines:
- Rufinamide or other medicines which decrease the QT interval on the heart tracing (ECG),
- Aprepitant, used to prevent nausea and vomiting by cancer treatment,
- Prednisone, used for rheumatoid arthritis,
- Pioglitazone, used for diabetes.

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines are still having the desired effect:
- Ciclosporin, tacrolimus and sirolimus, used to prevent rejection of a transplant,
- Cyclophosphamide, used for cancer,
- Digoxin, used to treat heart failure or an uneven heart beat,
- Colchicine, used for gout attack,

- Dabigatran etexilate, used to stop blood clots after hip or knee replacement surgery,
- Clarithromycin, used for bacterial infections,
- Saquinavir, fosamprenavir, indinavir, nevirapine, lopinavir/ritonavir combination, used for HIV,
- Alfentanil, fentanyl, used against strong pain,
- Vincristine, vinblastine, used for cancer,
- Mycophenolate mofetil (MMF), used in transplant patients,
- Midazolam, used for severe insomnia and stress,
- Bupropion, used for depression,
- Metformin, used for diabetes,
- Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan, used for different sorts of cancer.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Do not take CRESEMBA (Isavuconazole) if you are pregnant, unless your doctor tells you otherwise. This is because it is not known if it may affect or harm your unborn baby.

Do not breast-feed if you are taking CRESEMBA (Isavuconazole).

Driving and using machines
CRESEMBA (Isavuconazole) may make you feel confused, tired or sleepy. It can also make you pass out. Therefore, be very careful when driving or operating machines.

3. How to take CRESEMBA (Isavuconazole)

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Capsules:

Starting dose for the first two days (48 hours)
The recommended dose is two capsules every 8 hours.

Usual dose after the first two days
This is started 12 to 24 hours after your last starting dose. The recommended dose is two capsules once a day.

Capsules can be taken with or without food. Swallow the capsules whole. Do not chew, crush, dissolve or open the capsules.

Concentrate for solution for infusion:

CRESEMBA (Isavuconazole) will be given to you by a doctor or nurse.

Starting dose for the first two days (48 hours)
The recommended dose is one vial every 8 hours.

Usual dose after the first two days
This is started 12 to 24 hours after your last starting dose. The recommended dose is one vial once a day.

The vial will be given as a drip into a vein by your doctor or nurse.

You will be given the dose until your doctor tells you otherwise. The duration of treatment with CRESEMBA (Isavuconazole) for both capsules and infusion may be longer than 6 months if your doctor considers this necessary.

If you use more CRESEMBA (Isavuconazole) than you should
If you think you have been given too much CRESEMBA (Isavuconazole), talk to your doctor or nurse straight away. You may have more side effects such as:
- Headache, feeling dizzy, restless or sleepy,
- Tingling, reduced sense of touch or sensation in the mouth,
- Problems being aware of things, hot flushes, anxiety, joint pain,
- Changes in the way things taste, dry mouth, diarrhoea, vomiting,
- Feeling your heart beat, faster heart rate, being more sensitive to light.

If you forget to use CRESEMBA (Isavuconazole)

Capsule:
Take the capsules as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose.

Do not take a double dose to make up for a forgotten dose.

Concentrate for solution for infusion:
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, tell your doctor or nurse if you think that a dose has been forgotten.

If you stop using CRESEMBA (Isavuconazole)
CRESEMBA (Isavuconazole) treatment will continue for as long as your doctor tells you. This is to make sure that the fungal infection has gone.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using CRESEMBA (Isavuconazole) and tell your doctor straight away if you notice any of the following side effects:
- a severe allergic reaction (anaphylaxis) such as sudden wheezing, breathing problems, swelling of the face, lips, mouth or tongue, severe itching, sweating, dizziness or fainting, fast heartbeat or pounding in the chest.

Tell your doctor straight away if you notice any of the following side effects:
- Severe blistering of the skin, mouth, eyes or genitals.

Other side effects
Tell your doctor, if you notice any of the following side effects:

Common: may affect up to 1 in 10 people
- Low potassium in your blood,
- Decreased appetite,
- Hallucinations (delirium),
- Headache,
- Sleepiness (somnolence),
- Inflamed veins that could lead to blood clots (thrombophlebitis),
- Shortness of breath or sudden and severe difficulty breathing (dyspnoea),
- Feeling sick (nausea), being sick (vomiting), diarrhoea, stomach pain,
- Changes (increase) in blood tests of liver function,
- Rash, itching,
- Kidney failure (symptoms could include swelling of legs),
- Chest pain, feeling tired or sleepy,
- Problems where the injection was given.

Uncommon: may affect up to 1 in 100 people
- Reduced white blood cells - can increase your risk of infection and fever,
- Reduced blood cells called ‘platelets’ - can increase your risk for bleeding or bruising,
- Reduced red blood cells - can make you feel weak or short of breath or make your skin pale,
- Severe reduction in blood cells - can make you feel weak, cause bruising or make infections more likely,

- Rash, swelling of your lips, mouth, tongue or throat with difficulty breathing (hypersensitivity),
- Low blood sugar levels,
- Low blood levels of magnesium,
- Low levels in the blood of a protein called ‘albumin’,
- Not getting the right goodness from your diet (malnutrition),
- low blood levels of sodium (hyponatraemia),
- Depression, difficulty sleeping (insomnia),
- Seizure, fainting or feeling faint, dizziness,
- Sensation of tingling, tickling, or pricking of the skin (paraesthesia),
- Altered mental state (encephalopathy),
- Changes in taste (dysgeusia),
- Feeling of ‘spinning’ or being dizzy (vertigo),
- Heart beat problems - may be too fast or uneven, or extra heart beats – this may show in your heart tracing (electrocardiogram or ecg),
- Problems with the blood circulation (circulatory collapse),
- Low blood pressure (hypotension),
- Wheezing, very fast breathing, coughing up blood or blood-stained sputum (haemoptysis), nose bleeding (epistaxis),
- Indigestion,
- Constipation,
- Feeling bloated (abdominal distension),
- Enlarged liver (hepatomegaly),
- Inflammation of the liver (hepatitis),
- Problems with the skin, red or purple spots on the skin (petechiae), inflamed skin (dermatitis), hair loss (alopecia),
- Back pain,
- Swelling of the extremities,
- Feeling weak, very tired, or sleepy or generally out of sorts (malaise).

Side effects with frequency not known:
- A severe allergic reaction (anaphylaxis).

5. How to store CRESEMBA (Isavuconazole)

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store the vials in a refrigerator (2°C to 8°C). Store the capsules in a dry, well-ventilated place at a temperature not exceeding 30° C.

Protect from moisture.

Ask your doctor how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

Capsules:

What CRESEMBA (Isavuconazole) contains
- The active substance is isavuconazole. Each capsule contains 186.3 mg isavuconazonium sulfate, corresponding to 100 mg isavuconazole.
- The other ingredients are:
  - Capsule content: magnesium citrate (anhydrous), microcrystalline cellulose, talc, anhydrous colloidal silica, stearic acid.
  - Capsule shell: hypromellose, water, red iron oxide (E172) (capsule body only), titanium dioxide (E171), gellan gum, potassium acetate, disodium edetate, sodium laurilsulfate.
  - Printing ink: shellac, propylene glycol, potassium hydroxide, black iron oxide (E172).

What CRESEMBA (Isavuconazole) looks like and contents of the pack
CRESEMBA (Isavuconazole) 100 mg hard capsules are with a reddish-brown body marked with “100” in black ink and a white cap marked with “C” in black ink.

CRESEMBA (Isavuconazole) is available in cartons that contain 14 hard capsules (in two aluminum blisters), with each capsule pocket connected to a pocket with desiccant.

Do not puncture the blister containing the desiccant.

Do not swallow or use the desiccant.

Concentrate for solution for infusion:

What CRESEMBA (Isavuconazole) contains

- The active substance is isavuconazole. Each vial contains 372.6 mg isavuconazonium sulfate, corresponding to 200 mg isavuconazole.
- The other ingredients (excipients) are mannitol and sulfuric acid (for pH-adjustment).

What CRESEMBA (Isavuconazole) looks like and contents of the pack

CRESEMBA (Isavuconazole) 200 mg is presented in a sterile lyophilised white to yellow powder, in a single use glass vial, as a powder for concentrate for solution for infusion.

CRESEMBA (Isavuconazole) vial is available as one 10 mL Type I glass vial with rubber stopper and an aluminium cap with plastic seal.

Manufacturer

Almac Pharma Services Limited, Seagoe Industrial Estate, Craigavon, BT63 5UA, United Kingdom.

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