ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zokovea 125 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ensitrelvir fumaric acid equivalent to 125 mg of ensitrelvir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Approximately 9 mm round, white to light yellow white, tablets debossed on one side with the company logo and “711”, and “125” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zokovea is indicated for the post-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older.

Zokovea should be used in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Adults and adolescents aged 12 years and older
The recommended dose for patients 12 years and older is 375 mg of ensitrelvir orally once daily on Day 1 and 125 mg once daily from Days 2 to 5 for a total of 5 days.

It is recommended that administration should be started as soon as possible and within 72 hours following close contact with an individual who has SARS-CoV-2 infection (see section 5.1).

Missed dose
In case of missed dose, the patient should take it as soon as possible and resume the normal dosing schedule. If it is almost time for the next dose, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a forgotten one.

Special populations

Hepatic impairment
No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Zokovea is not recommended for use in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary in patients with renal impairment (see section 5.2).

Elderly
No dose adjustment is necessary in patients aged 65 years or older (see section 5.2).

Paediatric population
The safety and efficacy of Zokovea in children below 12 years of age has not yet been established. No data are available.

Method of administration

For oral use.

This medicinal product can be taken with or without food (see section 5.2). The tablets should be swallowed whole with water and not chewed, broken or crushed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnant women (see sections 4.4 and 4.6).

Medicinal products listed below are part of examples and are not considered a comprehensive list of all possible medicinal products that are contraindicated with ensitrelvir.

Medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions:
- Antianginal: ranolazine
- Antiarrhythmics: dronaderone, quinidine
- Anticancer agents: venetoclax (at the dose initiation and during the ramp-up phase in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma)
- Antigout agents: colchicine (in patients with renal and/or hepatic impairment)
- Antihistamines: terfenadine
- Antipsychotics: lurasidone, pimozide, quetiapine
- Antithrombotic agents: ticagrelor
- Cardiovascular medicinal products: eplerenone, ivabradine
- Cardiac myosin inhibitor: mavacamten (in patients with CYP2C19 poor metaboliser phenotype or undetermined CYP2C19 phenotype)
- Ergot derivatives: dihydroergotamine, ergotamine, methylergometrine
- GI motility agents: cisapride
- Immunosuppressants: voclosporin
- Lipid-modifying agents: simvastatin, lovastatin, lomitapide
- Mineralocorticoid receptor antagonists: finerenone
- Neuropsychiatric agents: cariprazine
- Opioid antagonists: naloxegol
- PDE5 inhibitors: avanafil, tadalafil when used for pulmonary arterial hypertension (PAH), vardenafil
- Sedative/hypnotics: daridorexant, oral midazolam, triazolam

Due to the long half-life of ensitrelvir and a time-dependent mechanism, the enzyme inhibiting effect on CYP3A may be maintained for 1-2 weeks following treatment with ensitrelvir.

Medicinal products that are potent CYP3A inducers where significantly reduced plasma concentrations of ensitrelvir may be associated with the potential loss of virologic response and potential resistance:
- Antibiotics: rifampicin

- Anticancer agents: apalutamide, enzalutamide, mitotane
- Anticonvulsants: carbamazepine, phenytoin
- Cystic fibrosis transmembrane conductance regulator potentiators: lumacaftor/ivacaftor
- Herbal products: St John's wort (*Hypericum perforatum*)

Zokovea should not be started immediately after discontinuation of potent CYP3A inducers due to the delayed offset of the recently discontinued CYP3A inducer (see section 4.5).

A multi-disciplinary approach (e.g, involving physicians and specialists in clinical pharmacology) should be considered to determine the adequate timing for Zokovea initiation taking into account the delayed offset of the recently discontinued CYP3A inducer and the need to initiate Zokovea within 72 hours following close contact with an individual who has SARS-CoV-2 infection (see section 4.2).

4.4 Special warnings and precautions for use

Women of childbearing potential

Women of childbearing potential have to use effective contraception. Pregnancy must be excluded before starting treatment (see sections 4.3 and 4.6).

Interaction with other medicinal products

Since ensitrelvir can interact with CYP3A inducers or medicinal products that are substrates of CYP3A, P-gp or BCRP, concomitant medicinal products should be carefully evaluated when prescribing Zokovea (see sections 4.3 and 4.5).

Hypersensitivity reactions

Anaphylaxis and anaphylactic shock have been reported with ensitrelvir (see section 4.8). If signs and symptoms of a clinically significant anaphylaxis occur, treatment should be discontinued immediately, and appropriate medications and/or supportive care should be initiated.

Severe hepatic impairment

No pharmacokinetic and clinical data are available in patients with severe hepatic impairment. Therefore, Zokovea is not recommended for use in patients with severe hepatic impairment.

Excipients with known effect

Sodium
Ensitrelvir tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free.'

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ensitrelvir

Ensitrelvir is a CYP3A, P-gp and BCRP substrate.

CYP induction
The strong CYP3A inducer carbamazepine (100 mg twice daily [Days 1 to 3], 200 mg twice daily [Days 4 to 6], 300 mg twice daily [Days 7 to 18]) decreased the AUC of ensitrelvir by 46%.

The effect of a moderate inducer is expected to be smaller, but a clinically relevant effect cannot be excluded.

Thus, co-administration of ensitrelvir with medicinal products that induce CYP3A may decrease plasma concentrations of ensitrelvir and reduce its therapeutic effect.

Concomitant use of potent CYP3A inducers with ensitrelvir is contraindicated (see section 4.3) and concomitant use of moderate CYP3A inducers with ensitrelvir is not recommended, but in case it is necessary, the prescriber should be aware that this may lead to a decreased exposure of ensitrelvir and a potential loss of virologic response.

CYP inhibition
The strong CYP3A inhibitor itraconazole (200 mg twice daily on Day 1 and then 200 mg once daily) increased the AUC of ensitrelvir by 1.31-fold. This is not considered clinically relevant, and ensitrelvir can be used with CYP3A inhibitors. Since itraconazole is also a P-gp and BCRP inhibitor, ensitrelvir can also be used with inhibitors of these transporters.

Effects of ensitrelvir on other medicinal products

Ensitrelvir is a strong CYP3A4 inhibitor.

CYP3A4 substrates
Zokovea is a strong CYP3A inhibitor since ensitrelvir 375/125 mg increased C_{max} and AUC of midazolam by 2.80- and 6.77-fold, respectively and increases plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Co-administration of ensitrelvir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see section 4.3).
Co-administration of other CYP3A substrates that may lead to potentially significant interactions (see Table 1) should be considered only if the benefit outweighs the risk.

P-glycoprotein substrates
Ensitrelvir (500 mg single dose) increased the C_{max} and $AUC_{0\text{-}inf}$ of the P-gp substrate digoxin by 2.17- and 1.31-fold, thus ensitrelvir is an inhibitor of P-gp. Caution should be exercised in case of concomitant treatment with sensitive P-gp substrates with narrow therapeutic index (e.g. digoxin, dabigatran). Close drug monitoring for safety and efficacy should be performed, and the dose may be adjusted accordingly.

BCRP substrates
Ensitrelvir (500 mg single dose) increased the C_{max} and $AUC_{0\text{-}inf}$ of the BCRP substrate rosuvastatin by 1.97- and 1.65-fold, thus ensitrelvir is an inhibitor of BCRP. Caution should be exercised in case of concomitant treatment with sensitive BCRP substrates with narrow therapeutic index.

OAT3 substrates
Based on *in vitro* studies, there is a potential for ensitrelvir to inhibit OAT3 at clinically relevant concentrations. No *in vivo* study has been performed. Caution should be exercised when OAT3 substrates with a narrow therapeutic index (e.g., methotrexate) are given concomitantly.

Oral contraceptives
The effects of the clinical dose of ensitrelvir on the PK of combined oral contraceptives (ethynyl estradiol and drospirenone) was investigated. Ensitrelvir did not affect the PK of ethynyl estradiol and increased the AUC of drospirenone by 1.81-fold. This is not considered clinically relevant.

Corticosteroids
The effect of ensitrelvir (750 mg on Day 1 and 250 mg on Days 2 to 5) on the pharmacokinetics of dexamethasone and prednisolone (both CYP3A4 substrates) were investigated. Dexamethasone exposure increased with co-administration of ensitrelvir and this effect decreased over time following the last dose of ensitrelvir. The C_{max} and $AUC_{0\text{-}inf}$ of dexamethasone on Day 5 increased 1.47-fold and 3.47-fold, those on day 9 increased 1.24-fold and 2.38-fold and those on Day 14 (10th day after the last ensitrelvir dose) increased 1.17-fold and 1.58-fold, compared to those following single-dose administration of dexamethasone alone. Caution is recommended in case of concomitant treatment

with dexamethasone. Administration of ensitrelvir did not have any clinically meaningful effect on the pharmacokinetics of prednisolone.

Substrates of CYP2B6, CYP2C8, CYP2C9 or CYP2C19
In vitro studies with ensitrelvir showed inhibitory effects on CYP2C8 and inductive effects on CYP2B6, CYP2C8, CYP2C9 and CYP2C19. No *in vivo* studies have been performed. Ensitrelvir might decrease exposure of substrates of CYP2B6 (e.g. bupropion), CYP2C9 (e.g. S-warfarin) and CYP2C19 (e.g. omeprazole). Additionally, ensitrelvir might either increase or decrease exposure of substrates of CYP2C8 (e.g. repaglinide).

Medicinal products listed in Table 1 are a guide and are not considered a comprehensive list of all possible medicinal products that are contraindicated or may interact with ensitrelvir.

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
Alpha$_1$-adrenoreceptor antagonist	↑ Alfuzosin	Concomitant use with ensitrelvir is not recommended since alfuzosin blood levels may be increased.
Alpha – Adrenergic receptor antagonist	↑ Silodosin	Concomitant use with ensitrelvir is not recommended since silodosin blood levels may be increased.
Analgesics (narcotic)	↑ Buprenorphine ↑ Fentanyl ↑ Methadone ↑ Oxycodone	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of these narcotic analgesics. If concomitant use with ensitrelvir is necessary, consider a dose reduction of these narcotic analgesics and closely monitor therapeutic and adverse effects (including respiratory depression). Refer to the individual SmPC for more information.
Antianginal	↑ Ranolazine	Co-administration is likely to result in increased plasma concentrations of ranolazine and is therefore contraindicated (see section 4.3).
Antiarrhythmics	↑ Dronedarone ↑ Quinidine	Co-administration is likely to result in increased plasma concentrations of dronedarone and quinidine and is therefore contraindicated (see section 4.3).
	↑ Disopyramide	Ensitrelvir may increase plasma concentrations of disopyramide which could result in an increased risk of adverse events such as cardiac arrhythmias. Caution is warranted and therapeutic concentration monitoring is recommended for disopyramide if available.

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
Antibiotics	↑ Erythromycin	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin is co-administered with ensitrelvir.
Anticancer drugs	↑ Apalutamide	Co-administration is contraindicated due to potential loss of virologic response of ensitrelvir, since apalutamide is a moderate to strong CYP3A4 inducer (see section 4.3). In addition, ensitrelvir may increase plasma concentrations of apalutamide which could result in the potential for serious adverse events including seizure.
	↑ Neratinib	Ensitrelvir may increase plasma concentrations of neratinib. Therefore, the co-administration of neratinib with ensitrelvir is not recommended. Refer to the neratinib SmPC for more information.
	Enzalutamide	Enzalutamide is a strong CYP3A4 inducer, and co-administration is contraindicated due to potential loss of virologic response (see section 4.3).
	↑ Axitinib ↑ Bortezomib ↑ Bosutinib ↑ Cabazitaxel ↑ Crizotinib ↑ Dasatinib ↑ Docetaxel ↑ Erlotinib ↑ Gefitinib ↑ Imatinib ↑ Irinotecan ↑ Lapatinib ↑ Nilotinib ↑ Panobinostat ↑ Ponatinib ↑ Ruxolitinib ↑ Sunitinib ↑ Temsirolimus	Ensitrelvir may increase plasma concentrations, resulting in the potential for increased incidence of adverse events. Refer to the individual SmPC for more information.
	Mitotane	Co-administration is contraindicated due to potential loss of virologic response (see section 4.3).

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
	↑ Ibrutinib	Plasma concentrations of ibrutinib may be increased due to CYP3A inhibition by ensitrelvir, resulting in increased risk for toxicity including risk of tumour lysis syndrome. Co-administration of ibrutinib and ensitrelvir should be avoided. If the benefit is considered to outweigh the risk and ensitrelvir must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity.
	↑ Venetoclax	Plasma concentrations may be increased due to CYP3A inhibition by ensitrelvir, resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase and is therefore contraindicated (see section 4.3). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons) when used with strong CYP3A inhibitors.
	↑ Ivosidenib	Ensitrelvir may increase plasma concentrations of ivosidenib, which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Ivosidenib is also a CYP3A inducer and this may lead to a decreased exposure of ensitrelvir and potential loss of virologic response. Co-administration should be avoided (refer to the ivosidenib SmPC for more information).
	↑ Vincristine ↑ Vinblastine	Plasma concentrations may be increased when co-administered with ensitrelvir resulting in the potential for increased incidence of adverse events.
Anticoagulants	↑ Apixaban	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of apixaban with ensitrelvir depend on the apixaban dose. For apixaban doses of 5 mg or 10 mg twice daily, reduce the apixaban dose by 50%. In patients already taking apixaban 2.5 mg twice daily, avoid co-administration with ensitrelvir.

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
	↑ Cilostazol	Plasma concentrations of cilostazol may be increased due to CYP3A inhibition by ensitrelvir. Dose adjustment of cilostazol is recommended. Refer to the cilostazol SmPC for more information.
	↑ Warfarin	It is recommended that anticoagulation parameters are monitored when warfarin is co-administered with ensitrelvir.
	↑ Dabigatran	Concomitant administration of ensitrelvir is expected to increase dabigatran concentrations (due to inhibition of P-gp) resulting in increased risk of bleeding. Reduce dose of dabigatran or avoid concomitant use.
	↑ Rivaroxaban	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ensitrelvir is not recommended in patients receiving rivaroxaban.
Anticonvulsants	Carbamazepine	Carbamazepine decreases AUC and C_{max} of ensitrelvir by up to 46% and 38%, respectively. Carbamazepine is a strong CYP3A4 inducer, and co-administration is contraindicated due to potential loss of virologic response (see section 4.3).
	Phenytoin	Phenytoin is a strong CYP3A4 inducer, and co-administration is contraindicated due to potential loss of virologic response (see section 4.3).
	Phenobarbital Primidone	Phenobarbital and primidone are moderate CYP3A4 inducers, and this may lead to a decreased exposure of ensitrelvir and potential loss of virologic response.
Antifungals	↑ Itraconazole	Itraconazole is a strong CYP3A4 inhibitor and increases AUC and C_{max} of ensitrelvir by 31% and 24%, respectively, which is not considered clinically relevant. Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when itraconazole is co-administered with ensitrelvir.

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
Antigout agents	↑ Colchicine	Concentrations of colchicine are expected to increase when co-administered with ensitrelvir due to CYP3A4 inhibition. Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions (see section 4.3). For patients with normal renal function, refer to colchicine SmPC.
Antihistamine	↑ Terfenadine	Increased plasma concentrations of terfenadine thereby, increasing the risk of serious arrhythmias from this agent. Therefore, concomitant use with ensitrelvir is contraindicated (see section 4.3).
Antimycobacterials	Rifampicin	Rifampicin is a strong CYP3A4 inducer, and co-administration is contraindicated due to potential loss of virologic response (see section 4.3).
	↑ Rifabutin	An increase in rifabutin exposure is expected due to the inhibition of CYP3A by ensitrelvir.
Antipsychotics	↑ Lurasidone ↑ Pimozide ↑ Quetiapine	Co-administration is likely to result in increased plasma concentrations of lurasidone, pimozide, quetiapine, and is therefore contraindicated (see section 4.3).
	↑ Aripiprazole	Dose adjustment of aripiprazole is recommended since ensitrelvir is expected to increase plasma concentrations of aripiprazole due to CYP3A inhibition. Refer to aripiprazole SmPCs for more information.
	↑ Haloperidol	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of haloperidol.
Antithrombotics	↑ Ticagrelor	Co-administration is contraindicated (see section 4.3).
Beta-adrenoceptor agonists (long acting)	↑ Salmeterol	Ensitrelvir inhibits CYP3A and as a result a pronounced increase in the plasma concentrations of salmeterol is expected, resulting in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Therefore, avoid concomitant use with ensitrelvir.

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
Calcium channel blockers	↑ Amlodipine ↑ Felodipine ↑ Nifedipine ↑ Verapamil	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of calcium channel antagonists. If co-administered, patients should be carefully monitored for therapeutic and adverse effects during the co-administration. Refer to individual calcium channel antagonist SmPCs for more information.
Cardiac glycosides	↑ Digoxin (31%, 117%)	This interaction is due to modification of P-gp mediated digoxin efflux by ensitrelvir. Monitor digoxin levels if possible and digoxin safety and efficacy.
Cardiovascular drugs	↑ Eplerenone ↑ Ivabradine	Co-administration is contraindicated (see section 4.3).
	↑ Guanfacine	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of guanfacine. Dose adjustment is recommended, refer to guanfacine SmPC.
	↑ Mavacamten	Co-administration in patients with CYP2C19 poor metaboliser phenotype or undetermined CYP2C19 phenotype is contraindicated (see section 4.3).
	↑ Riociguat	Plasma concentrations may be increased due to CYP3A and P-gp inhibition by ensitrelvir. The co-administration of riociguat with ensitrelvir is not recommended.
Corticosteroids	↑ Budesonide ↑ Ciclesonide ↑ Dexamethasone (247%, 47%) ↑ Methylprednisolone	Ensitrelvir inhibits CYP3A and increases the plasma concentrations of dexamethasone. It is also expected to increase the plasma concentrations of budesonide, ciclesonide, and methylprednisolone. Caution is recommended in case of concomitant use, refer to individual SmPCs.
Cystic fibrosis transmembrane conductance regulator potentiators	Lumacaftor/ivacaftor	Lumacaftor/ivacaftor is a strong CYP3A4 inducer, and co-administration is contraindicated (see section 4.3).
Disease modifying anti-rheumatic drug	↑ Methotrexate	Ensitrelvir may inhibit OAT3 and as a result is expected to increase the plasma concentrations of methotrexate. Caution should be exercised in case of concomitant treatment.
Dopamine agonists	↑ Bromocriptine	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of bromocriptine.

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
Ergot derivatives	↑ Dihydroergotamine ↑ Ergotamine ↑ Methylergometrine	Co-administration is contraindicated due to potential for acute ergot toxicity characterised by vasospasm and ischemia of the extremities and other tissues, including the central nervous system (see section 4.3).
Gastrointestinal drugs	↑ Aprepitant ↑ Loperamide	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of aprepitant and loperamide.
GI motility agent	↑ Cisapride	Ensitrelvir may increase plasma concentrations of cisapride thereby, increasing the risk of serious arrhythmias from this agent and therefore concomitant use with ensitrelvir is contraindicated (see section 4.3).
Herbal products (for depression)	St. John's wort	Herbal preparations containing St John's wort (*Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of ensitrelvir and therefore concomitant use with ensitrelvir is contraindicated (see section 4.3).
HIV CCR5 antagonist	↑ Maraviroc	Ensitrelvir is expected to increase the plasma levels of maraviroc as a result of CYP3A inhibition. For further information, refer to the SmPC for maraviroc.
HIV non-nucleoside reverse transcriptase inhibitors	Efavirenz Etravirine	Efavirenz and etravirine are moderate CYP3A4 inducers, and this may lead to a decreased exposure of ensitrelvir and potential loss of virologic response.
HMG-CoA reductase inhibitors (Statins)	↑ Lovastatin ↑ Simvastatin	Co-administration is contraindicated (see section 4.3).
	↑ Atorvastatin	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of atorvastatin (refer to atorvastatin SmPC).
	↑ Rosuvastatin (65%, 97%)	Ensitrelvir inhibits BCRP and as a result increases the plasma concentrations of rosuvastatin (refer to rosuvastatin SmPC).
Hyperparathyroidism therapies	↑ Cinacalcet	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of cinacalcet. Dose adjustments may be needed.
Immunosuppressants	↑ Voclosporin	Co-administration is contraindicated due to potential for acute and/or chronic nephrotoxicity (see section 4.3).

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
	Calcineurin inhibitors: ↑ Cyclosporine ↑ Tacrolimus	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of cyclosporine and tacrolimus. This co-administration should only be considered with close and regular monitoring of immunosuppressant blood concentrations, to reduce the dose of the immunosuppressant in accordance with the latest guidelines and to avoid over-exposure and subsequent increase of serious adverse reactions of the immunosuppressant. It is important that the close and regular monitoring is performed not only during the co-administration with ensitrelvir but is also pursued after the treatment with ensitrelvir.
	↑ Everolimus ↑ Sirolimus	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of everolimus and sirolimus. This co-administration should only be considered with close and regular monitoring of immunosuppressant blood concentrations, to reduce the dose of the immunosuppressant in accordance with the latest guidelines and to avoid over-exposure and subsequent increase of serious adverse reactions of the immunosuppressant. It is important that the close and regular monitoring is performed not only during the co-administration with ensitrelvir but is also pursued after the treatment with ensitrelvir.
Janus kinase (JAK) inhibitors	↑ Tofacitinib	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of tofacitinib. Dose adjustment of tofacitinib is recommended. Refer to the tofacitinib SmPC for more information.
Microsomal triglyceride transfer protein (MTTP) inhibitors	↑ Lomitapide	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of lomitapide. Co-administration is contraindicated due to potential for hepatotoxicity (see section 4.3).
Migraine medications	↑ Eletriptan	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of eletriptan. Ensitrelvir should not be used with eletriptan.

Table 1. Interaction with other medicinal products and other forms of interaction

Medicinal product class	Medicinal product within class (AUC change, C_{max} change)	Clinical comments
Mineralocorticoid receptor antagonists	↑ Finerenone	Co-administration is contraindicated due to potential for serious adverse reactions, including hyperkalaemia, hypotension, and hyponatremia (see section 4.3).
Neuropsychiatric agents	↑ Cariprazine	Co-administration is contraindicated due to increased plasma exposure of cariprazine and its active metabolites (see section 4.3).
Opioid antagonists	↑ Naloxegol	Co-administration contraindicated due to the potential for opioid withdrawal symptoms (see section 4.3).
PDE5 inhibitors for pulmonary arterial hypertension	↑ Tadalafil	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of tadalafil. Co-administration is contraindicated (see section 4.3).
PDE5 inhibitors for erectile dysfunction	↑ Avanafil ↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of avanafil, sildenafil, tadalafil, and vardenafil. Co-administration with avanafil and vardenafil is contraindicated (see section 4.3).
Sedatives	↑ Triazolam	Co-administration is contraindicated (see section 4.3).
Sedatives/hypnotics	↑ Daridorexant	Co--administration is contraindicated (see section 4.3).
	↑ Zopiclone	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of zopiclone. Dose adjustments may be needed.
	↑ Oral midazolam (577%, 180%)	Ensitrelvir inhibits CYP3A and as a result increases the plasma concentrations of midazolam. Co-administration with oral midazolam is contraindicated (see section 4.3). Caution should be taken in case of co-administration with parenteral midazolam.
Selective vasopressin V2-receptor antagonists	↑ Tolvaptan	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of tolvaptan. Dose reduction of tolvaptan is recommended for patients. Refer to the tolvaptan SmPC for more information.
Urologic drugs	↑ Oxybutynin	Ensitrelvir inhibits CYP3A and as a result is expected to increase the plasma concentrations of oxybutynin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Women of childbearing potential have to use effective contraception during treatment with ensitrelvir and for 2 weeks after the last dose of ensitrelvir (see sections 5.2 and 5.3). Pregnancy must be excluded before starting treatment.

Pregnancy

There is a limited amount of data from the use of ensitrelvir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Ensitrelvir is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether ensitrelvir is excreted in human milk. A non-clinical study in rats has shown that ensitrelvir is excreted in milk (see section 5.3). A risk to the suckling child cannot be excluded. Therefore, breast-feeding is not recommended during treatment and for 2 weeks after the last dose of ensitrelvir (see section 5.2).

Fertility

The effect of ensitrelvir on fertility in humans has not been studied. Based on animal study data, there is no evidence that ensitrelvir has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Zokovea has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are hypertriglyceridaemia (5.4%), headache (2.7%), diarrhoea (1.9%) and nausea (1.1%).

The most serious adverse reactions are anaphylaxis and anaphylactic shock (frequency not known).

Tabulated list of adverse reactions

The safety profile of the product is based on adverse reactions reported in clinical trials and spontaneous reporting. The adverse reactions in Table 2 below are listed by system organ class and frequency. Frequencies are 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); not known (frequency cannot be estimated from the available data).

Table 2. Adverse reactions

	Very common	**Common**	**Uncommon**	**Rare**	**Frequency not known***
Immune system disorders					Anaphylaxis, Anaphylactic shock
Metabolism and nutrition disorders		Hypertriglyceridaemia	Dyslipidaemia		

	Very common	Common	Uncommon	Rare	Frequency not known*
Hepatobiliary disorders			Hyperbilirub-inaemia		
Nervous system disorders		Headache			
Gastrointestinal disorders		Diarrhoea, Nausea	Vomiting, Abdominal discomfort, Dyspepsia		
Skin and subcutaneous tissue disorders			Rash, Eczema, Urticaria, Pruritus	Drug eruption	

*Post-marketing data

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 reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote for Zokovea. In the event of overdose, general supportive measures should be initiated based on the patient's signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, protease inhibitors, ATC code: J05AE16.

Mechanism of action

Ensitrelvir selectively inhibits SARS-CoV-2 3C-like (3CL) protease, an essential enzyme for the processing of the polyprotein encoded by the SARS-CoV-2 gene, which thereby inhibits SARS-CoV-2 replication. The 50% inhibitory concentration (IC_{50}) of ensitrelvir for SARS-CoV-2 3CL protease activity was 0.0132 μmol/L.

Antiviral activity

The antiviral activity of ensitrelvir against clinical isolates of SARS-CoV-2 including viral strains with mutations in the spike protein such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Theta (P.3), Lambda (C.37), Mu (B.1.621) and Omicron (B.1.1.529) strain was determined using VeroE6/TMPRSS2 cells. The 50% effective concentration (EC_{50}) of ensitrelvir for SARS-CoV-2 ranged from 0.20 to 0.99 μmol/L.

Amino acid substitutions of D48G, M49L, P52S, S144A, and M49L/S144A of SARS-CoV-2 nsp5 region were identified after virus passage in the presence of ensitrelvir *in vitro*. Fold change values of ensitrelvir against recombinant SARS-CoV-2 carrying D48G, M49L, P52S, S144A, and M49L/S144A were 4.3, 17, 3.7, 9.2, and 100, respectively.

In study 2206T1331, a total of 51 participants had the nsp5 sequence data available at post-dose out of 243 participants with a positive PCR post-dose (central laboratory) in the ensitrelvir group of the mITT population, 1030 participants. Out of 51 participants, the ensitrelvir TEAASs in the nsp5 were detected in 19 participants: M49L in 10 participants, T25A in 4 participants, M49I in 3 participants and P52S in 3 participants (including 1 participant with M49L and T25A).

Fold change values of ensitrelvir against recombinant SARS-CoV-2 carrying T25A, M49I, M49L and P52S were 14.4, 5.3, 17 and 3.7, respectively.

Definition of ensitrelvir TEAAS: Amino acid substitution confirmed ≥ 3 participants who experience treatment-emergent amino acid substitutions with a mutation frequency ≥ 15% and ≥ 2.5 fold (relative to placebo) in the proportion of participants with treatment-emergent amino acid substitution with mutation frequency ≥ 15% in either of ensitrelvir groups in the ITT population.

Pharmacodynamic effects

No QTc prolongation was observed at the plasma concentration range of ensitrelvir by using concentration-QTc analysis based on the data after single doses of ensitrelvir 20 to 2000 mg.

Clinical efficacy

Study 2206T1331
This was a phase 3 multicentre, double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of ensitrelvir in the prevention of symptomatic SARS-CoV-2 infection in household contacts of an individual within 72 hours with symptomatic COVID-19. The study was conducted in the following countries: Argentina, Japan, South Africa, United States and Vietnam. Eligible participants (12 years and older) were randomly assigned to either the ensitrelvir group or placebo group (1:1).

- Ensitrelvir group:
  As a loading dose, 375 mg was administered on Day 1. Thereafter, as a maintenance dose, 125 mg was administered on Days 2 to 5.
- Placebo group:
  Matching placebo was administered once daily for 5 days.

A total of 2387 participants were randomised, and 2041 participants were included in the mITT set. The mITT set was defined as all randomised and dosed participants who had a confirmed negative screening SARS-CoV-2 RT-PCR result (central laboratory).

The % of males was 43.3% ensitrelvir and 38.0% placebo and % of females was 56.7% ensitrelvir and 62.0% placebo. The % of 12 to < 18 year olds was 6.2% ensitrelvir and 5.3% placebo; % of 18 to 64 year olds was 84.2% ensitrelvir and 85.8% placebo and % of 65 year olds and older was 9.6% ensitrelvir and 8.9% placebo.

Symptomatic COVID-19 was defined as a Central Laboratory Confirmed -positive RT-PCR test and the occurrence (or worsening [increasing a symptom score from baseline] in the case of pre-existing COVID-19-like symptoms) of ≥ 1 of the 14 specified COVID-19 symptoms for at least 48 hours.

The primary endpoint, the proportion of participants with symptomatic COVID-19 through Day 10 (95% CI) in the mITT population, was 2.9% (30/1030; 95% CI: 1.97%, 4.13%) in the ensitrelvir group and 9.0% (91/1011; 95% CI: 7.31%, 10.94%) in the placebo group. The risk ratio of symptomatic COVID-19 in participants randomised to ensitrelvir compared to participants who randomised to placebo was 0.33 (0.22, 0.49) ($p < 0.0001$).

In an unadjusted descriptive subgroup analysis by geographic region, symptomatic COVID-19 through Day 10 occurred in 11 of 266 participants (4.1%; 95% CI: 2.08%, 7.28%) in the ensitrelvir group and 62 of 270 participants (23.0%; 95% CI: 18.08%, 28.45%) in the placebo group in Japan, corresponding to a risk ratio of 0.18 (95% CI: 0.10, 0.33). In North America, symptomatic COVID-19 through Day 10 occurred in 15 of 692 participants (2.2%; 95% CI: 1.22%, 3.55%) in the ensitrelvir group and 25 of 683 participants (3.7%; 95% CI: 2.38%, 5.36%) in the placebo group, corresponding to a risk ratio of 0.60 (95% CI: 0.32, 1.12). In the Rest of World subgroup (Argentina, South Africa and Vietnam), symptomatic COVID-19 through Day 10 occurred in 4 of 72 participants (5.6%; 95% CI: 1.53%, 13.62%) in the ensitrelvir group and 4 of 58 participants (6.9%; 95% CI: 1.91%, 16.73%) in the placebo group, corresponding to a risk ratio of 0.84 (95% CI: 0.27, 2.61).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Zokovea in one or more subsets of the paediatric population for the post-exposure prophylaxis of COVID-19 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration of ensitrelvir once daily with a loading dose of 375 mg on Day 1 and a maintenance dose of 125 mg on Days 2 to 5, the geometric mean (CV%) ensitrelvir C_{max} and $AUC_{0-\tau}$ on Day 1 were 19.7 (21.1%) µg/mL and 325.0 (15.7%) µg·hr/mL, respectively, and those on Day 5 were 24.8 (13.4%) µg/mL and 475.5 (15.0%) µg·hr/mL, respectively. The median time to C_{max} (T_{max}) is 2.75 to 3.25 hours. The absolute bioavailability of ensitrelvir has not been established.

Effect of food on oral absorption
In healthy adults who received single oral administration of ensitrelvir 375 mg in the fed state (after a high fat high caloric breakfast), the AUC increased by approximately 25% and the median T_{max} was delayed from 2.50 hours (in the fasted state) to 6.00 hours (in the fed state), but did not influence the C_{max} of ensitrelvir. There was no clinically meaningful difference in the exposure of ensitrelvir between the fasted and fed states, although T_{max} is delayed in the fed state compared to the fasted state.

Distribution

The human serum protein binding ratio is 97.7% to 98.7%.

The geometric mean apparent volume of distribution in the terminal elimination phase was from 13.5 to 20.6 L after single oral administration of ensitrelvir (suspension) 20 to 2000 mg in the fasted state to Japanese healthy adult male participants.

Biotransformation

An *in vitro* study revealed that multiple CYP enzymes including CYP3A contributed to form ensitrelvir triazole N-desmethyl.

When ensitrelvir was orally administered with a single dose in the fasted state for healthy adults, mainly unchanged ensitrelvir was detected in plasma and chlorinated metabolite of ensitrelvir was detected as a metabolite in plasma. Minor metabolites were observed in the urine (ensitrelvir triazole N-desmethyl, ensitrelvir indazole N-desmethyl, and an unknown metabolite1) and faeces (N-deindazolated form of ensitrelvir, ensitrelvir triazole N-desmethyl, ensitrelvir indazole N-desmethyl, ensitrelvir 3-indazolinone, ensitrelvir indazole 4-Cl, and another unknown metabolite 2).

Elimination

The majority of elimination of ensitrelvir is via the biliary route with some contribution from renal elimination. Following [^{14}C]-ensitrelvir (suspension) was administered orally at a dose of 375 mg to healthy participants, approximately 65% and 26% of ensitrelvir was recovered in faeces and urine. Unchanged ensitrelvir was mainly detected in the plasma, which was approximately 90% of the total radioactivity in the plasma.

Following oral administration of ensitrelvir once daily with a loading dose of 375 mg on Day 1 and a maintenance dose of 125 mg on Days 2 to 5, the geometric mean terminal elimination half-life on Day 5 was 58 hours.

Linearity/non-linearity

Ensitrelvir exhibited almost linear pharmacokinetics in the fasted state within the dose range of 20 mg to 2000 mg (suspension) in healthy adult volunteers.

Special populations

In a population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of ensitrelvir were observed based on age (12 to 91 years of age), gender, or race/ethnicity.

Elderly
The exposure in elderly participants aged ≥ 65 years of age was comparable to that in healthy adult participants.

Body weight
There was a trend towards higher exposure for lower body weight, but this was not considered clinically relevant.

Paediatric population
Pharmacokinetic studies have not been performed with ensitrelvir in infants and children under 12 years of age (see section 4.2).

The adolescents who received ensitrelvir ranged in weight from 32 kg to 112 kg. Pharmacokinetic analyses confirmed ensitrelvir exposures in adolescents were comparable to those of adults.

Renal impairment
Pharmacokinetic studies have been performed with ensitrelvir in patients with renal impairment. Compared to healthy controls with no renal impairment, the C_{max} and AUC_{inf} of ensitrelvir increased by 1.32- and 1.44-fold in patients with mild renal impairment, 1.33- and 1.49-fold in patients with moderate renal impairment, and 1.11- and 1.60-fold in patients with severe renal impairment, respectively.

Renal impairment does not have a clinically meaningful effect on the pharmacokinetics of ensitrelvir (see section 4.2).

Hepatic impairment
Pharmacokinetic studies have been performed with ensitrelvir in patients with mild to moderate hepatic impairment.

Compared to healthy controls with no hepatic impairment, the C_{max} and AUC_{inf} of ensitrelvir was 0.89-, and 1.03-fold in patients with mild hepatic impairment, 0.74- and 0.87-fold in patients with moderate hepatic impairment, respectively. Therefore, mild and moderate hepatic impairment does not have a clinically meaningful effect on the pharmacokinetics of ensitrelvir (see section 4.2).

Pharmacokinetic studies have not been performed with ensitrelvir in patients with severe hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Based on the results of non-clinical general toxicity studies, the adverse effects of ensitrelvir include decreased food consumption, decreased erythrocyte parameters, inflammatory changes in multiple organs, decreased platelet count and vomiting. The findings are observed at 2 to 3-fold higher exposure than the clinical exposure dose. In the 2 and 4 week oral toxicity study in monkeys, infiltration by inflammatory cells, mainly mononuclear cells, was observed in the hepatic portal vein, gallbladder, lung/bronchus at a dose equivalent to 8.0 times or more than the clinical exposure dose.

No carcinogenicity studies have been conducted with ensitrelvir.

Ensitrelvir did not affect male and female fertility and early embryo development in rats at doses up to a dose equivalent 8.2 to 10 times the clinical exposure dose.

In an embryo-foetal development study in rats, ensitrelvir did not induce malformations or embryo-foetal lethality up to a dose equivalent 6.6 times the clinical exposure dose. However, low food consumption and body weight in dams and slight foetal growth retardation and high frequency of short supernumerary rib were noted at 1000 mg/kg/day a dose equivalent 6.6 times the clinical exposure dose.

In an embryo-foetal development study in rabbits, ensitrelvir induced embyo-foetal lethality or malformation with severe maternal toxicity by continuous administration at doses equivalent to 5.0 and 7.4 times the clinical exposure dose, respectively during rabbit organogenesis. The changes noted at doses equivalent to 5.0 and 7.4 times the clinical exposure dose, respectively, were malformations of the axial skeleton, the changes associated with vertebral malformations such as skeletal variations of the thoracic centrum, and short tail, and high frequencies of full supernumerary rib and/or supernumerary lumbar vertebra as skeletal variation. In addition, abortion associated with maternal toxicity was observed in 1 dam at doses equivalent to 5.0 times the clinical exposure dose.

In a pre-and postnatal developmental and maternal function study in rats a decrease in survival rate on postnatal day 4 and growth retardation were observed in the pups at a dose equivalent 6.6 times the clinical exposure dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Croscarmellose sodium (E468)
Hydroxypropyl cellulose (E463)
Silica, colloidal anhydrous (E551)
Microcrystalline cellulose (E460)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE with Aluminium foil blisters.

Carton containing a blister strip with a total of 7 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Herengracht 464,
1017 CA,
Amsterdam,
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2062/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Shionogi B.V.
Herengracht 464
Amsterdam
1017 CA
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zokovea 125 mg tablets
ensitrelvir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains ensitrelvir fumaric acid equivalent to 125 mg of ensitrelvir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

7 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

Do not chew, break or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. EXPIRY DATE

EXP

8. SPECIAL STORAGE CONDITIONS

9. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

10. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Herengracht 464,
1017CA,
Amsterdam,
The Netherlands

11. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2062/001

12. BATCH NUMBER

Lot

13. INFORMATION IN BRAILLE

Zokovea 125 mg tablets

14. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

15. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zokovea 125 mg tablets
ensitrelvir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shionogi and company logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zokovea 125 mg tablets
ensitrelvir

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zokovea is and what it is used for

Zokovea contains the active substance ensitrelvir. This is a medicine that helps to fight viral infections throughout the whole body. This is an antiviral medicine used in adults and adolescents 12 years and older to prevent COVID-19 after exposure to SARS-CoV-2, the virus that causes the disease.

COVID-19 is caused by a virus called a coronavirus. Zokovea stops the virus multiplying in cells, which in turn stops the virus multiplying in the body. This can help your body overcome the virus infection and may prevent you from developing severe illness.

2. What you need to know before you take Zokovea

Do not take Zokovea if:
- you are allergic to ensitrelvir or any of the other ingredients of this medicine (listed in section 6).
- you are pregnant.
- you are using any of the following medicines, since taking them with Zokovea may cause serious or life-threatening side effects or affect how Zokovea **works**:
  - Quinidine, dronaderone, ranolazine (for irregular heart rhythm)
  - Colchicine (for gout)
  - Pimozide (for severe tics)
  - Lurasidone, cariprazine (for schizophrenia)
  - Quetiapine (for bipolar disorder)
  - Ticagrelor (for preventing blood clots)
  - Eplerenone, ivabradine, mavacamten (for heart problems)
  - Dihydroergotamine, ergotamine, methylergometrine (for headaches)
  - Voclosporin (for supressing the immune system)

- Simvastatin, lomitapide and lovastatin (for high cholesterol)
- Finerenone (for chronic kidney disease)
- Tadalafil (for pulmonary arterial hypertension)
- Triazolam, oral midazolam and daridorexant (for sleeping problems)
- Venetoclax, apalutamide, enzalutamide, and mitotane (for cancer)
- Carbamazepine and phenytoin (for epilepsy)
- Rifampicin (for some serious infections including tuberculosis)
- Lumacaftor and ivacaftor (for cystic fibrosis)
- St John's wort (*Hypericum perforatum;* a herbal medicine for depression and anxiety)
- Terfenadine (antihistamines)
- Naloxegol and cisapride (for constipation)
- Avanafil and vardenafil (for male erectile dysfunction)

Warnings and precautions

Allergic reactions
Allergic reactions, including severe allergic reactions (known as 'anaphylaxis'), can happen in people taking Zokovea – even after only 1 dose.

Liver disease
Tell your doctor if you have or have had a liver disease.

Children and adolescents
Do not give Zokovea to children under 12 years because this medicinal product has not been studied in this age group.

Other medicines and Zokovea
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those used for:

Blood and heart (cardiovascular) diseases:
- uneven heartbeats, such as disopyramide
- high blood pressure, such as amlodipine, nifedipine, felodipine, verapamil
- heart problems, such as guanfacine, riociguant, digoxin
- high blood cholesterol, such as atorvastatin, rosuvastatin

Infectious diseases:
- infections, such as erythromycin, rifabutin (antibiotics)
- fungal infections, such as itraconazole (anti-fungals)
- HIV infection, such as maraviroc, efavirenz, etravirine

Mental health conditions:
- mental or mood disorders, such as haloperidol, aripiprazole
- psychosis such as bromocriptine (dopamine receptor agonists)
- stress such as zopiclone, parenteral midazolam (sedatives and hypnotics)

Inflammatory diseases:
- inflammation, such as budesonide, ciclesonide, dexamethasone, methylprednisolone (steroids and corticosteroids)
- rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or ulcerative colitis, such as tofacitinib, methotrexate

Other diseases:
- severe pain, such as fentanyl, oxycodone, methadone, buprenorphine
- lung problems, such as salmeterol
- kidney disease, such as cinacalcet, tolvaptan

- digestive problems, such as aprepitant, loperamide
- overactive bladder, such as tolterodine, oxybutynin
- erectile dysfunction (also known as impotence) such as sildenafil, tadalafil
- cancer, such as docetaxel, temsirolimus, gefitinib, dasatinib, erlotinib, lapatinib, bortezomib, imatinib, sunitinib, bosutinib, cabazitaxel, crizotinib, panobinostat, ponatinib ruxolitinib, axitinib, nilotinib, irinotecan, vincristine, vinblastine, ibrutinib, neratinib
- autoimmune disease or organ transplant, such as cyclosporine, tacrolimus, everolimus, sirolimus
- epilepsy (seizures), such as phenobarbital, primidone
- headaches, such as eletriptan
- thinning the blood (anti-coagulants), such as warfarin, apixaban, cilostazol, dabigatran, rivaroxaban
- benign prostatic hyperplasia such as alfuzosin, silodosin

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Many medicines interact with ensitrelvir. **Keep a list of your medicines** to show your doctor and pharmacist.

Do not start taking a new medicine without telling your doctor or pharmacist, they can tell you if it is safe to take Zokovea with other medicines.

Pregnancy, breast-feeding and fertility

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

Do not take Zokovea if you are pregnant.

Women of childbearing potential have to use effective contraception (birth control) during treatment with ensitrelvir and for two weeks after the last dose of ensitrelvir. Pregnancy should be ruled out before starting treatment.

You should not breast-feed your baby while taking Zokovea, and for 2 weeks after stopping Zokovea as a precaution. This is because there is no information on the use of Zokovea in breast-feeding and it is not known whether the medicine passes into breast milk.

Driving and using machines

Zokovea is not expected to influence the ability to drive and use machines.

Zokovea contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Zokovea

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

How much to take

A course of treatment lasts 5 days.
The recommended dose is:

- day 1: take 3 tablets at the same time (total dose 375 mg)
- days 2, 3, 4 and 5: take 1 tablet per day (125 mg)

How to take

Zokovea should be taken as soon as possible and within 72 hours following close contact with an individual who has COVID-19.

Zokovea can be taken with or without food:
- Swallow the tablets whole with water
- Do not chew, break, or crush the tablets.

If you take more Zokovea than you should

If you take too much Zokovea, call your doctor or pharmacist straight away or go to the nearest hospital emergency room straight away.

If you forget to take Zokovea

If you forget a dose, take it as soon as you remember it. However, if it is almost time for the next dose, do not take the missed dose and take your next normal dose at its scheduled time. Do not take a double dose to make up for a forgotten one.

If you stop taking Zokovea

Even if you feel better, do not stop taking this medicine without talking to your doctor. However, you should stop taking this medicine if you have signs of a serious allergic reaction as stated in leaflet section 4.

If you have any questions about this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Serious side effects:

Stop taking Zokovea and contact a doctor or go to your nearest emergency department **immediately** if you experience any of the following symptoms:

Signs of a serious allergic reaction (frequency not known)
- trouble swallowing or breathing
- swelling of the tongue, mouth, and face
- tight throat
- a hoarse voice
- itching
- skin rash

Other side effects:

Talk to your doctor if you notice any of the following side effects:

Common (may affect up to 1 in 10 people)
- headache

- diarrhoea
- feeling sick (nausea)
- increased blood levels of certain fats (lipids) called triglycerides

Uncommon (may affect up to 1 in 100 people)
- increased levels of a substance produced by the liver (bilirubin) in the blood
- vomiting
- stomach (abdominal) discomfort
- indigestion (dyspepsia)
- skin rash
- eczema
- itchy rash (urticaria)
- itchy skin (pruritus)

Rare (may affect up to 1 in 1000 people)
- skin allergy as rash, redness and small raised bumps (drug eruption)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Zokovea

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 carton or the blister after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zokovea contains

The active substance is ensitrelvir. Each tablet contains ensitrelvir fumaric acid, equivalent to 125 mg of ensitrelvir.

The other excipients are mannitol (E421), croscarmellose sodium (E468), hydroxypropyl cellulose (E463), silica colloidal anhydrous (E551), microcrystalline cellulose (E460) and magnesium stearate (E470b).

What Zokovea looks like and contents of the pack

Approximately 9 mm round, white to light yellow white, tablets debossed on one side with the company logo and "711", and "125" on the other side.

Zokovea is packaged in a carton containing a PVC/PCTFE blister strip with a total of 7 tablets.

Marketing Authorisation Holder

Shionogi B.V.
Herengracht 464,
1017 CA,
Amsterdam,
The Netherlands

Manufacturer

Shionogi B.V.
Herengracht 464,
1017 CA,
Amsterdam,
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu