LIVTENCITY▼ (maribavir) tablets 200mg

REDEFINING POST-TRANSPLANT REFRACTORY CMV TREATMENT

LIVTENCITY▼ (maribavir) is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).[1]

Consideration should be given to official guidance on the appropriate use of antiviral agents.[1]

▼ This medicinal product is subject to additional monitoring. Adverse events should be reported. Reporting forms and information can be found at: **www.mhra.gov.uk/yellowcard**

Adverse events should also be reported to Takeda at: **AE.GBR-IRL@takeda.com**

Prescribing Information can be accessed on page 9

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MECHANISM OF ACTION

CMV is one of the most common infections experienced by transplant recipients, with an estimated incidence rate of 16–56% in SOT recipients and 30–70% in HSCT recipients.[2,3]

Transplant recipients with CMV infection have a higher risk of numerous clinical complications, contributing to increased morbidity and mortality.[4]

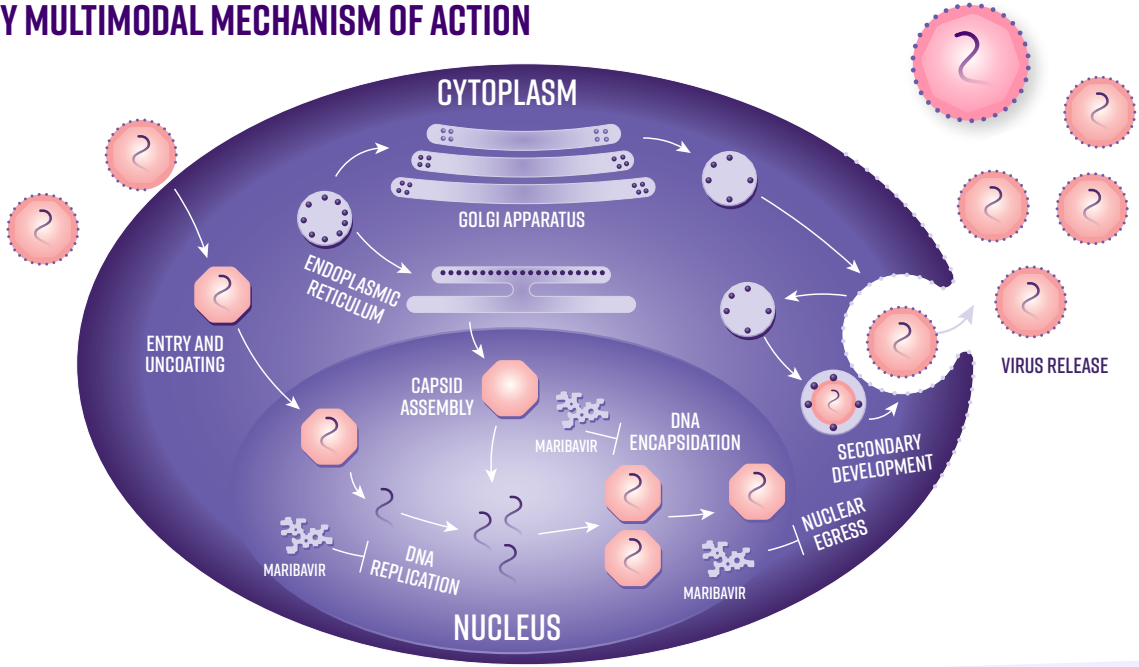
Current management can lead to resistance, graft rejection, neutropenia, and nephrotoxicity.[5] Furthermore, prolonged antiviral exposure and sub-therapeutic drug levels can increase the risk of CMV infections becoming refractory (with or without resistance).[6,7]

LIVTENCITY is an anti-CMV agent indicated for the treatment of refractory (with or without resistance) CMV infections in adult transplant recipients.[1] LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).

LIVTENCITY has a differentiated, **multimodal mechanism of action** from current CMV antivirals that competitively inhibits the CMV-specific UL97 protein kinase[1,8], resulting in the downstream inhibition of CMV:[9,10]

○ **DNA replication** ○ **Viral encapsidation** ○ **Nuclear egress of viral capsids**

LIVTENCITY MULTIMODAL MECHANISM OF ACTION



LIVTENCITY MET PRIMARY ENDPOINT AND KEY SECONDARY ENDPOINT IN THE PHASE 3 SOLSTICE TRIAL[8]

LIVTENCITY was evaluated in SOLSTICE – a multicentre, randomised, open-label, active-controlled superiority trial in patients who received SOT (n=211) or HSCT (n=141) with refractory (with or without resistance) CMV to one or a combination of the investigator-assigned therapies (IATs): ganciclovir, valganciclovir, foscarnet, or cidofovir.[1,8]

Eligible patients were randomised 2:1 to receive LIVTENCITY 400 mg orally BID or IAT (valganciclovir/ganciclovir, foscarnet, or cidofovir) for 8 weeks.[1,8]

SOLSTICE PRIMARY ENDPOINT

Confirmed CMV viraemia clearance* compared to IAT at the end of Study Week 8[1,8]

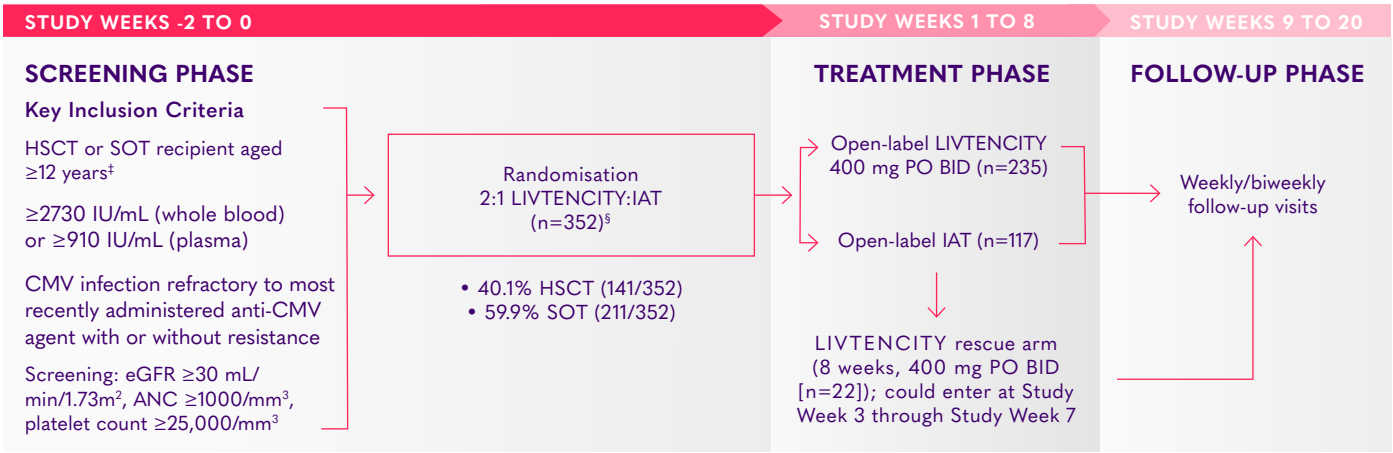
SOLSTICE KEY SECONDARY ENDPOINT

Achievement of CMV viraemia clearance* and symptom control† at the end of Study Week 8, maintained through Study Week 16[1,8]

SOLSTICE SAFETY ENDPOINTS

Safety endpoints included treatment-emergent adverse events (TEAEs) and serious TEAEs (TESAEs).[8]

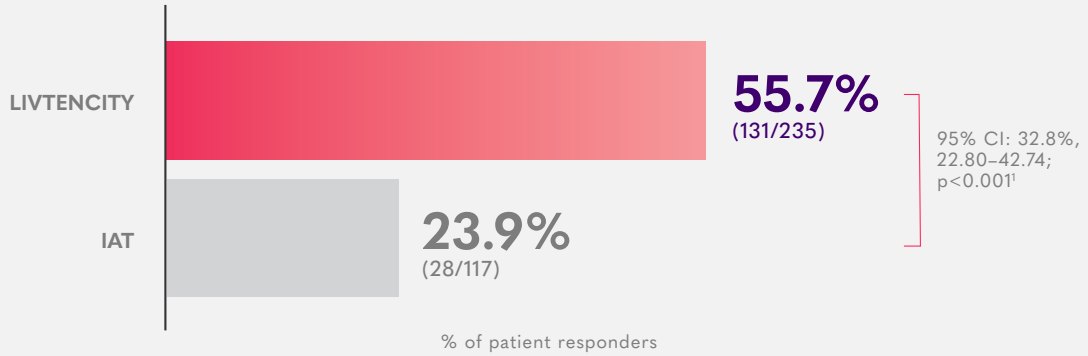
STUDY DESIGN[8,II]



*CMV viraemia clearance = plasma CMV DNA < lower limit of quantification (i.e. <137 IU/mL) in two consecutive tests ≥5 days apart.
†CMV infection symptom control was defined as resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic patients at baseline, or no new symptoms for patients who were asymptomatic at baseline.
‡Although the inclusion criterion was ≥12 years, all patients were >18 years old.
§Additional stratification by baseline CMV DNA level (high, intermediate, and low) and transplant type.

IN THE PIVOTAL PHASE 3 TRIAL, LIVTENCITY DELIVERED DOUBLE THE VIRAEMIA CLEARANCE (55.7%) COMPARED TO IAT (23.9%): PRIMARY ENDPOINT[1,8]

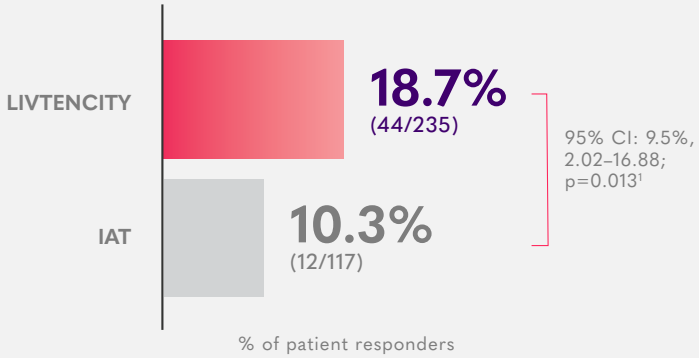
PRIMARY ENDPOINT: CONFIRMED VIRAEMIA CLEARANCE* OF REFRACTORY (WITH OR WITHOUT RESISTANCE) CMV IN ALL TRANSPLANTS (HSCT AND SOT) AT STUDY WEEK 8 VS IAT[1,8]



*Confirmed viraemia clearance = plasma CMV DNA < lower limit of quantification (i.e. <137 IU/mL) in 2 consecutive tests ≥5 days apart.

IN THE PIVOTAL PHASE 3 TRIAL, LIVTENCITY DELIVERED ALMOST DOUBLE THE VIRAEMIA CLEARANCE AND SYMPTOM CONTROL AT STUDY WEEK 8 MAINTAINED THROUGH WEEK 16 (18.7%) COMPARED TO IAT (10.3%): KEY SECONDARY ENDPOINT[1,8]

KEY SECONDARY ENDPOINT: CONFIRMED CMV VIRAEMIA CLEARANCE* AND SYMPTOM CONTROL† IN ALL TRANSPLANTS (HSCT AND SOT) AT THE END OF STUDY WEEK 8, MAINTAINED THROUGH STUDY WEEK 16 VS IAT[1,8]



*Confirmed viraemia clearance = plasma CMV DNA < lower limit of quantification (i.e. <137 IU/mL) in 2 consecutive tests ≥5 days apart.
†CMV infection symptom control was defined as resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic patients at baseline, or no new symptoms for patients who were asymptomatic at baseline.

MOST COMMONLY REPORTED ADVERSE REACTIONS OCCURRING IN AT LEAST 10% OF SUBJECTS IN THE LIVTENCITY GROUP*[I]

ADVERSE REACTION	FREQUENCY (n=234)
Taste disturbance†	46%
Nausea	21%
Diarrhoea	19%
Vomiting	14%
Fatigue	12%

The most commonly-reported serious adverse reactions were diarrhoea (2%) and nausea, weight decreased, fatigue, immunosuppressant drug concentration level increased, and vomiting (all occurring at >1%).[1]

TASTE DISTURBANCE† RARELY LED TO DISCONTINUATION OF LIVTENCITY[8,II]

IN THE SOLSTICE TRIAL, THE MOST REPORTED TREATMENT-RELATED AE WAS DYSGEUSIA:

35.9% (84/234)

vs 0.9% (1/116) receiving IAT that typically resolved during or after treatment

IN THE SOLSTICE TRIAL, DYSGEUSIA RARELY LED TO TREATMENT DISCONTINUATION:

0.9% (2/234)

discontinued due to dysgeusia in LIVTENCITY group

*Adverse events were collected during the treatment phase and follow-up phase through Study Week 20 in the Phase 3 study.
†Taste disturbance comprised of the reported preferred terms ageusia, dysgeusia, hypogeusia and taste disorder.

TWICE-DAILY ORAL ADMINISTRATION

The recommended dose of LIVTENCITY is 400 mg (2 x 200 mg tablets) twice-daily, resulting in a daily dose of 800 mg for 8 weeks[1]

Treatment duration may need to be individualised based on the clinical characteristics of each patient.[1]

Patients should skip a missed dose if the next dose is due within the next 3 hours, and continue with the regular schedule. Patients should not double their next dose or take more than the prescribed dose.[1]

CAN BE TAKEN WITH OR WITHOUT FOOD

LIVTENCITY can be taken with or without food and the film-coated tablet can be taken as a whole tablet, a crushed tablet, or a crushed tablet through a nasogastric or orogastric tube.[1]

NO RENAL OR HEPATIC DOSE ADJUSTMENTS*

LIVTENCITY does not require dose adjustment for renal impairment, mild or moderate hepatic impairment, or patients over 65 years. Dose adjustment to 1200 mg BID is recommended when co-administered with the anticonvulsants carbamazepine, phenobarbital and phenytoin.[1]

Please refer to the LIVTENCITY Summary of Product Characteristics for further details on interactions and dose recommendations with other medicinal products.

*Administration of LIVTENCITY in patients with end-stage renal disease, including patients on dialysis, has not been studied. No dose adjustment is expected to be required for patients on dialysis due to the high plasma protein binding of LIVTENCITY. Administration of LIVTENCITY in patients with severe hepatic impairment has not been studied. It is not known whether exposure to LIVTENCITY will significantly increase in patients with severe hepatic impairment. Therefore, caution is advised when LIVTENCITY is administered to patients with severe hepatic impairment.

IMMUNOSUPPRESSANT LEVELS[1]

LIVTENCITY has the potential to increase the drug concentrations of immunosuppressants that are cytochrome P450 (CYP)3A/P-gp substrates with narrow therapeutic margins, including:

- **Tacrolimus**
- **Cyclosporine**
- **Sirolimus**
- **Everolimus**

The plasma levels of these immunosuppressants must be frequently monitored throughout treatment with LIVTENCITY and doses should be adjusted as needed. **Especially following initiation and after discontinuation of LIVTENCITY.**

ANTAGONISTIC EFFECT[1]

LIVTENCITY may antagonise the antiviral effect of ganciclovir and valganciclovir by inhibiting human CMV UL97 protein kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir. Co-administration of LIVTENCITY with ganciclovir or valganciclovir is contraindicated.

Please refer to the LIVTENCITY Summary of Product Characteristics for further details on the effect of other medicinal products on LIVTENCITY, and the effect of LIVTENCITY on other medicinal products.

ABBREVIATIONS

AE = adverse event; ANC = absolute neutrophil count; BID = twice daily; CI = confidence interval; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; HSCT = haematopoietic stem cell transplant; IAT = investigator-assigned therapy; IU = international unit; PO = orally; SOT = solid organ transplant; TEAEs = treatment emergent adverse events; TESAEs = treatment emergent serious adverse events; UL = unique long.

REFERENCES

1. LIVTENCITY UK Summaries of Product Characteristics [GB & NI].
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3. Cho SY, et al. Int J Mol Sci. 2019;20(11):2666.
4. Azevedo LS, et al. Clinics (Sao Paulo). 2015;70(7):515–23.
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7. El Chaer F, et al. Blood. 2016;128(23):2624–36.
8. Avery RK, et al. Clin Infect Dis. 2022;75(4):690–701.
9. Papanicolaou GA, et al. Clin Infect Dis. 2019;68:1255–64.
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IN THE PIVOTAL PHASE 3 TRIAL, TWICE-DAILY ORAL DOSING WITH LIVTENCITY DEMONSTRATES:

- **TWICE THE EFFICACY OF IAT*:** 55.7% (131/235) of transplant recipients receiving LIVTENCITY had confirmed CMV viraemia clearance† (vs 23.9% [28/117] receiving IAT; p<0.001; primary endpoint met)[1,8]
- **LOWER INCIDENCE OF NEUTROPENIA COMPARED TO VALGANCICLOVIR/GANCICLOVIR:** 1.7% of transplant recipients treated with LIVTENCITY experienced treatment-related neutropenia (vs 25% in those who received valganciclovir/ganciclovir)‡[1,8,11]
- **LOWER INCIDENCE OF ACUTE KIDNEY INJURY (AKI) COMPARED TO FOSCARNET:** 1.7% of transplant recipients treated with LIVTENCITY experienced treatment-related acute kidney injury (vs 19.1% in those who received foscarnet)‡[8,11]
- **HIGHER INCIDENCE OF DYSGEUSIA COMPARED TO THE IAT ARM:** 35.9% (84/234) of transplant recipients treated with LIVTENCITY experienced treatment-related dysgeusia (vs 0.9% [1/116] in those who received IAT)‡[1,11]

PRESCRIBING INFORMATION

Click here to access prescribing information for Northern Ireland Click here to access prescribing information for Great Britain

*IAT = one or a combination of ganciclovir, valganciclovir, foscarnet, or cidofovir.
†Confirmed viraemia clearance = plasma CMV DNA < lower limit of quantification (i.e. <137 IU/mL) in 2 consecutive tests ≥5 days apart.
‡Reported in ≥5% of patients.[11]

Intended for UK healthcare professionals only.

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