Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

10 May 2021

HON. FRANCISCO T. DUQUE III, MD, MSc
Secretary of Health

Dear **Secretary Duque:**

Greetings!

This has reference to the request of the Disease Prevention and Control Bureau (DPCB) dated 29 March 2021 for the evaluation of the COVID-19 investigational drugs namely, remdesivir, tocilizumab, baricitinib, and favipiravir.

In light of the developments on COVID-19 investigational drugs, the Health Technology Assessment Council (HTAC) adopts the results of rapid reviews for evidence of the efficacy of the Living Clinical Practice Guidelines (LCPG) Group.

The following regulatory information and evidence considered by the HTAC for the assessment of COVID-19 investigational drugs were as follows:

- Annex A: Summary Table of COVID-19 Investigational Drugs
- Annex B: Product Quality based on the FDA Certificate of Product Registration (CPR);
- Annex C: Clinical efficacy and safety; and
- Annex D: Cost-analysis.

According to the Philippine Food and Drug Administration (FDA), tocilizumab and baricitinib have Certificates of Product Registration (CPRs) for rheumatoid arthritis while remdesivir and favipiravir have ongoing applications for Emergency Use Authorization. We would like to reiterate that proper regulatory authorization must be secured for the emergency use and procurement of these drugs.

Relative thereto, the HTAC **recommends the use** of the following drugs for the following indications:

COVID-19 Investigational Drug	Recommendation
Remdesivir	In addition to dexamethasone, among COVID-19 patients who have oxygen saturation of < 94% and/or requiring oxygen supplementation but are not on high flow nasal cannula or mechanical ventilation.
Tocilizumab	In addition to systemic steroids, in patients showing respiratory deterioration and/or requiring high doses of oxygen and with elevated markers of inflammation

Baricitinib	In combination with remdesivir, in hospitalized patients with COVID-19 who cannot take corticosteroids and require oxygen supplementation.

On the other hand, HTAC recommends **against the use** of the following drugs for the following populations:

COVID-19 Investigational Drug	Recommendation
Remdesivir	Among patients who (a) do not require oxygen supplementation and have oxygen saturation of ≥ 94%, and (b) are on HFNC or mechanical ventilation except in a clinical trial setting.
Tocilizumab	Among patients with COVID-19 infection who do not require oxygen supplementation.

Meanwhile, there is *insufficient evidence* at this point to recommend the use of *favipiravir* to patients diagnosed with COVID-19.

The recommendations above are interim for emergency use of the investigational drugs to COVID-19 patients. However, this is not indicative of the inclusion of the above-mentioned drugs in the Philippine National Formulary (PNF) because there is a need to have a separate application in compliance with documentary requirements.

HTAC is actively on the watch for evidence as it is rapidly evolving, and shall update its recommendation when new information becomes available.

Further, we recommend that the Department of Health (DOH) secure appropriate regulatory authorization for remdesivir, tocilizumab, and baricitinib from the FDA for the procurement and/or reimbursement by the DOH and PhilHealth.

Should you have questions or clarifications, please do not hesitate to let us know them. We remain grateful for the opportunity to work with you. Thank you very much and best regards.

Respectfully yours,

For the Health Technology Assessment Council (HTAC):

Marita V. T-Reyes

MARITA V. TOLENTINO-REYES, MD
Chair, HTAC

Approval of the HTAC Recommendation:

FRANCISCO T. DUQUE III, MD, MSc
Secretary of Health

CC: Undersecretary Gerardo V. Bayugo, MD, MPH, CESO I
Assistant Secretary Atty. Charade B. Mercado-Grande

Evidence

- Annex A: Summary table for COVID-19 Investigational Drugs
- Annex B: Product Quality based on the FDA Certificate of Product Registration (CPR)
- Annex C: Clinical efficacy and safety
    - Remdesivir
    - Tocilizumab
    - Baricitinib
    - Favipiravir
- Annex D: Cost analysis

ANNEX A. SUMMARY TABLE FOR COVID-19 INVESTIGATIONAL DRUGS

Investigational drugs	Emergency Use Authorization (EUA)/Drugs under Emergency Use (DEU)	Certificate of Product Registration (CPR)	Listed in the Philippine National Formulary (PNF)	FDA-Listed Forms, Dosage, and Indications	2021 LCPG Group Recommendation
Remdesivir	Ongoing EUA application	None	No	Not applicable	- Recommends the use of remdesivir, in addition to dexamethasone, among COVID-19 patients who have oxygen saturation of less than 94% and/or requiring oxygen supplementation but are not on high-flow nasal cannula (HFNC) or mechanical ventilation. - Against the use of remdesivir among patients who (a) do not require oxygen supplementation and with oxygen saturation of ≥ 94%, and (b) are on HFNC or mechanical ventilation.
Tocilizumab	- Per FDA, no need for EAU application as the drug already has a CPR - Eligible to register under DEU	Yes	No	**Forms and dosage strength:** ● 400 mg/20 mL Concentrate Solution for IV Infusion; ● 200 mg/10 mL Concentrate Solution for IV Infusion; ● 80 mg/4 mL Concentrate	- Recommends the addition of tocilizumab to systemic steroids in patients showing respiratory deterioration and/or requiring high doses of oxygen and with elevated markers of inflammation.

				Solution for IV • Infusion; and • 162 mg/0.9 mL Solution for Injection (SC) **Indication:** Rheumatoid arthritis	- Against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen.
Baricitinib	- Per FDA, no need for EAU application as the drug already has a CPR - Eligible to register under DEU	Yes	No	**Forms and dosage strength:** 2 mg and 4 mg film-coated tablet **Indications**: Treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded adequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. It may be used as monotherapy or in combination with methotrexate.	Recommends the use of baricitinib in combination with remdesivir in hospitalized COVID-19 patients requiring oxygen supplementation and who take corticosteroids. However, there is no evidence to recommend the use of baricitinib alone in hospitalized COVID-19 patients
Favipiravir	Ongoing EUA application	None	No	Not applicable	There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19 unless in the context of a clinical trial.

ANNEX B: PRODUCT QUALITY BASED ON THE FDA CERTIFICATE OF PRODUCT REGISTRATION (CPR)

Certificate of Product Registration of Tocilizumab (80 mg/4 ml [20 mg/ml] Concentrate for Solution for I.V. Infusion)

FDA-2018IAR3TYFTNYTSEA2GVCEN

Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City, Alabang, Muntinlupa City

FDA Food and Drug Administration PHILIPPINES

CERTIFICATE OF PRODUCT REGISTRATION

Pursuant to the provisions of Republic Act (R.A.) No. 3720 as amended, known as the Foods, Drugs, Devices and Cosmetics Act, and consistent with R.A. No. 6675, known as the Generics Act of 1988, and R.A. No. 9711, otherwise known as the Food and Drug Administration Act of 2009, the product described hereunder has been found to conform with the requirements and standards for marketing authorization of pharmaceutical products per existing regulations in force as of date hereof.

Registration Number	:	**BR-690**
Generic Name	:	Tocilizumab
Brand Name	:	Actemra
Dosage Strength & Form	:	80 mg/4 mL (20 mg/mL) Concentrate for Solution for I.V. Infusion
Pharmacologic Category	:	Interleukin Inhibitor
Classification	:	Prescription Drug (Rx)
Approved Shelf-life	:	30 months
Storage Condition	:	Store between 2-8°C. Do not freeze.
Packaging	:	20 mL Type I colorless glass vial (Box of 1's)
Manufacturer	:	Chugai Pharma Manufacturing Co., 16-3, Kiyohara Kogyodanchi, Utsunomiya City, Tochigi, Japan
For	:	F. Hoffman-La Roche Ltd. Basel, Switzerland
Importer	:	Roche (Philippines), Inc. Unit 1804 & 19th Floor, One Global Place Building, 5th Avenue corner 25th Street, Bonifacio Global City, Taguig City
Distributor	:	Zuellig Pharma Corporation Km. 14 West Service Road, South Super Highway corner Edison Avenue, Brgy. Sun Valley, Parañaque City

The marketing authorization shall be valid until **20 March 2023** subject to the conditions listed on the reverse side. No change in the formulation, labelling and commercial presentation of this product shall be made at any time during the effectivity of this registration without prior written approval of this Office.

This marketing authorization is subject to suspension, cancellation or recall should any violation of R.A. No. 3720, R.A. No. 6675 and R.A. No. 9711 and/or regulations issued thereunder involving the product be committed.

Witness My Hand and Seal of this Office, this **18 June 2018**.

By Authority of the Director General
Per FDA Order No. 2016-005

ATTY. KATHERINE M. AUSTRIA-LOCK
Officer-in-Charge
Center for Drug Regulation and Research

REG. STATUS	:	Renewal
AMOUNT	:	Php 12,650.00
OR NUMBER	:	0978996
DATE	:	08 February 2018
CODE	:	438-110-218
BAR CODE DOC TRACK	:	2018020110730

FDA-0296845

Certificate of Product Registration of Tocilizumab (200 mg/10 ml [20 mg/ml] Concentrate for Solution for I.V. Infusion)

FDA-2018SY8KE7TAI28MGWXSEYLL

Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City, Alabang, Muntinlupa City

CERTIFICATE OF PRODUCT REGISTRATION

. Pursuant to the provisions of Republic Act (R.A.) No. 3720 as amended, known as the Foods, Drugs, Devices and Cosmetics Act, and consistent with R.A. No. 6675, known as the Generics Act of 1988, and R.A. No. 9711, otherwise known as the Food and Drug Administration Act of 2009, the product described hereunder has been found to conform with the requirements and standards for marketing authorization of pharmaceutical products per existing regulations in force as of date hereof.

Registration Number	:	**BR-691**
Generic Name	:	Tocilizumab
Brand Name	:	Actemra
Dosage Strength & Form	:	200 mg/10 mL (20 mg/mL) Concentrate for Solution for I.V. Infusion
Pharmacologic Category	:	Interleukin Inhibitor
Classification	:	Prescription Drug (Rx)
Approved Shelf-life	:	30 months
Storage Condition	:	Store between 2-8°C. Do not freeze.
Packaging	:	20 mL Type I colorless glass vial (Box of 1's)
Manufacturer	:	Chugai Pharma Manufacturing Co., Ltd. 16-3, Kiyohara Kogyodanchi, Utsunomiya City, Tochigi, Japan
For	:	F. Hoffman-La Roche Ltd. Basel, Switzerland
Importer	:	Roche (Philippines), Inc. Unit 1804 & 19th Floor, One Global Place Building, 5th Avenue corner 25th Street, Bonifacio Global City, Taguig City
Distributor	:	Zuellig Pharma Corporation Km. 14 West Service Road, South Super Highway corner Edison Avenue, Brgy. Sun Valley, Parañaque City

The marketing authorization shall be valid until **20 March 2023** subject to the conditions listed on the reverse side. No change in the formulation, labelling and commercial presentation of this product shall be made at any time during the effectivity of this registration without prior written approval of this Office.

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Witness My Hand and Seal of this Office, this **18 June 2018**.

By Authority of the Director General
Per FDA Order No. 2016-005

ATTY. KATHERINE M. AUSTRIA-LOCK
Officer-in-Charge
Center for Drug Regulation and Research

REG. STATUS : Renewal
AMOUNT : Php 12,650.00
OR NUMBER : 0978997
DATE : 08 February 2018
CODE : 438.110.218
BAR CODE : 2018020110075 2
DOC TRACK :

FDA-0296847

Certificate of Product Registration of Tocilizumab (400 mg/20 ml [20 mg/ml] Concentrate for Solution for I.V. Infusion)

FDA-201849YOII1SBYNXK1M2ERY9

Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City, Alabang, Muntinlupa City

CERTIFICATE OF PRODUCT REGISTRATION

Pursuant to the provisions of Republic Act (R.A.) No. 3720 as amended, known as the Foods, Drugs, Devices and Cosmetics Act, and consistent with R.A. No. 6675, known as the Generics Act of 1988, and R.A. No. 9711, otherwise known as the Food and Drug Administration Act of 2009, the product described hereunder has been found to conform with the requirements and standards for marketing authorization of pharmaceutical products per existing regulations in force as of date hereof.

Registration Number	:	**BR-689**
Generic Name	:	Tocilizumab
Brand Name	:	Actemra
Dosage Strength & Form	:	400 mg/20 mL (20 mg/mL) Concentrate for Solution for I.V. Infusion
Pharmacologic Category	:	Interleukin Inhibitor
Classification	:	Prescription Drug (Rx)
Approved Shelf-life	:	30 months
Storage Condition	:	Store between 2-8°C. Do not freeze.
Packaging	:	20 mL Type I colorless glass vial (Box of 1's)
Manufacturer	:	Chugai Pharma Manufacturing Co., Ltd. 16-3, Kiyohara Kogyodanchi, Utsunomiya City, Tochigi, Japan
For	:	F. Hoffman-La Roche Ltd Basel, Switzerland
Importer	:	Roche (Philippines), Inc. Unit 1804 & 19th Floor, One Global Place Building, 5th Avenue corner 25th Street, Bonifacio Global City, Taguig City
Distributor	:	Zuellig Pharma Corporation Km. 14 West Service Road, South Super Highway corner Edison Avenue, Brgy. Sun Valley, Parañaque City

The marketing authorization shall be valid until **20 March 2023** subject to the conditions listed on the reverse side. No change in the formulation, labelling and commercial presentation of this product shall be made at any time during the effectivity of this registration without prior written approval of this Office.

This marketing authorization is subject to suspension, cancellation or recall should any violation of R.A. No. 3720, R.A. No. 6675 and R.A. No. 9711 and/or regulations issued thereunder involving the product be committed.

Witness My Hand and Seal of this Office, this **18 June 2018**.

By Authority of the Director General
Per FDA Order No. 2016-005

ATTY. KATHERINE M. AUSTRIA-LOCK
Officer-in-Charge
Center for Drug Regulation and Research

REG. STATUS	:	Renewal
AMOUNT	:	Php 12,650.00
OR NUMBER	:	0978998
DATE	:	08 February 2018
CODE	:	438.110.218
BAR CODE DOC TRACK	:	2018020110815

FDA-0296846

Certificate of Product Registration of Baricitinib (2 mg film-coated tablet)

FDA-2019IBDEGAE48TANHI5SHIIK

Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City, Alabang, Muntinlupa City

FDA Food and Drug Administration PHILIPPINES

CERTIFICATE OF PRODUCT REGISTRATION

Pursuant to the provisions of Republic Act (R.A.) No. 3720 as amended, known as the Foods, Drugs, Devices and Cosmetics Act, and consistent with R.A. No. 6675, known as the Generics Act of 1988, and R.A. No. 9711, otherwise known as the Food and Drug Administration Act of 2009, the product described hereunder has been found to conform with the requirements and standards for marketing authorization of pharmaceutical products per existing regulations in force as of date hereof.

Registration Number	:	**DR-XY46772**
Generic Name	:	Baricitinib
Brand Name	:	Olumiant
Dosage Strength & Form	:	2 mg Film-Coated Tablet
Pharmacologic Category	:	Selective Immunosuppressants
Classification	:	Prescription drug (Rx)
Approved Shelf-life	:	36 months
Storage Condition	:	Store at temperatures not exceeding 30°C
Packaging	:	Cold formable aluminum foil with aluminum foil lidding blister pack x 7's (Box of 7's. 14's and 28's)
Manufacturer	:	Lilly del Caribe, Inc. 12.6 KM 65th Infantry Road, Carolina, Puerto Rico, PR00985, United States of America
Packer	:	Lilly, S.A. Avda De La Industria, 30, Alcobendas, 28108 Madrid, Spain
Importer/Distributor	:	Eli Lilly (Philippines) Inc. Unit 401-403 Tower 1, Rockwell Business Center, Ortigas Avenue, Pasig City

The marketing authorization shall be valid until **28 November 2024** subject to the conditions listed on the reverse side. No change in the formulation, labelling and commercial presentation of this product shall be made at any time during the effectivity of this registration without prior written approval of this Office.

This marketing authorization is subject to suspension, cancellation or recall should any violation of R.A. No. 3720, R.A. No. 6675 and R.A. No. 9711 and/or regulations issued thereunder involving the product be committed.

Witness My Hand and Seal of this Office, this **28 November 2019**.

By Authority of the Director-General
Per FDA Order No. 2016-005

ATTY. KATHERINE M. AUSTRIA-LOCK
Officer-in-Charge
Center for Drug Regulation and Research

REG. STATUS	:	Monitored Release
AMOUNT	:	Php 45,960.00
OR NUMBER	:	871303
DATE	:	18 Jul 2017
CODE	:	311/234
BAR CODE / DOC TRACK	:	2 0 1 7 0 7 0 5 1 6 3 7 3 8

TÜVRheinland CERTIFIED Management System ISO 9001:2015

FDA-0446164

Certificate of Product Registration of Baricitinib (4 mg film-coated tablet)

FDA-2019GSTB58TG5Y2EBE479I7V

Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City, Alabang, Muntinlupa City

FDA Food and Drug Administration PHILIPPINES

CERTIFICATE OF PRODUCT REGISTRATION

Pursuant to the provisions of Republic Act (R.A.) No. 3720 as amended, known as the Foods, Drugs, Devices and Cosmetics Act, and consistent with R.A. No. 6675, known as the Generics Act of 1988, and R.A. No. 9711, otherwise known as the Food and Drug Administration Act of 2009, the product described hereunder has been found to conform with the requirements and standards for marketing authorization of pharmaceutical products per existing regulations in force as of date hereof.

Registration Number	:	**DR-XY46773**
Generic Name	:	Baricitinib
Brand Name	:	Olumiant
Dosage Strength & Form	:	4 mg Film-Coated Tablet
Pharmacologic Category	:	Selective Immunosuppressants
Classification	:	Prescription drug (Rx)
Approved Shelf-life	:	36 months
Storage Condition	:	Store at temperatures not exceeding 30°C
Packaging	:	Cold formable aluminum foil with aluminum foil lidding blister pack x 7's (Box of 7's. 14's and 28's)
Manufacturer	:	Lilly del Caribe, Inc. 12.6 KM 65th Infantry Road, Carolina, Puerto Rico, PR00985, United States of America
Packer	:	Lilly, S.A. Avda De La Industria, 30, Alcobendas, 28108 Madrid, Spain
Importer/Distributor	:	Eli Lilly (Philippines) Inc. Unit 401-403 Tower 1, Rockwell Business Center, Ortigas Avenue, Pasig City

The marketing authorization shall be valid until **28 November 2024** subject to the conditions listed on the reverse side. No change in the formulation, labelling and commercial presentation of this product shall be made at any time during the effectivity of this registration without prior written approval of this Office.

This marketing authorization is subject to suspension, cancellation or recall should any violation of R.A. No. 3720, R.A. No. 6675 and R.A. No. 9711 and/or regulations issued thereunder involving the product be committed.

Witness My Hand and Seal of this Office, this **28 November 2019**.

By Authority of the Director-General
Per FDA Order No. 2016-005

ATTY. KATHERINE M. AUSTRIA-LOCK
Officer-in-Charge
Center for Drug Regulation and Research

REG. STATUS : Monitored Release
AMOUNT : Php 45,960.00
OR NUMBER : 871304
DATE : 18 Jul 2017
CODE : 311/234
BAR CODE / DOC TRACK : 2017070516374 1

TÜVRheinland CERTIFIED Management System ISO 9001:2015

FDA-0446165

ANNEX C. CLINICAL EFFICACY AND SAFETY

Data on clinical efficacy and safety of COVID-19 investigational drugs

COVID-19 Investigational Drugs	Data on clinical efficacy and safety (Source: 2021 Rapid reviews from the Philippine COVID-19 Living Clinical Practice Guidelines Group)
Remdesivir	*Summary of Evidence* ● Four randomized controlled trials (n=7,345) on the use of remdesivir as treatment for COVI-19 were found. Low quality evidence shows that remdesivir has limited effect on all cause-mortality [relative risk: 0.93 (95% CI: 0.82 to 1.06)], clinical improvement [relative risk: 1.06 (95%CI: 0.99 to 1.13)], and initiation of mechanical ventilation among confirmed COVID-19 patients relative risk: 0.64 (95% CI: 0.38 to 1.07)]. ● However, remdesivir appears to be beneficial in the time to clinical improvement especially among cases needing supplemental oxygen [rate ratio: 1.45 (95% CI 1.18 to 1.79)] but not on high flow oxygen [rate ratio: 1.09 (95%CI 0.76 to 1.57)] mechanical ventilation [rate ratio: 0.98 (95% CI 0.70 to 1.37)]. ● Remdesivir did not show increased risk for serious adverse events [(relative risk: 0.74, 95% CI: 0.62 to 0.88)]. Availability and cost of intervention should be considered before making recommendations regarding its use locally. *Recommendations* ● Among COVID-19 patients with O2 saturation ≥94% and do not require oxygen supplementation, we suggest against the use of remdesivir. ○ Level of Evidence: Low ○ Strength of Recommendation: Conditional ● In addition to dexamethasone, among patients with COVID-19 infection who have O2 saturation <94% and/or requiring oxygen supplementation but are not on high flow oxygen or mechanical ventilation, we suggest the use of remdesivir. ○ Level of Evidence: Low ○ Strength of Recommendation: Conditional ● Among patients with COVID-19 infection who are on high flow oxygen or mechanical ventilation, we suggest against the use of remdesivir. ○ Level of Evidence: Low ○ Strength of Recommendation: Conditional *Consensus issues* ● Early introduction of remdesivir in the treatment of COVID-19 is preferred because of its action on the polymerase resulting in less viral replication. ● Remdesivir is a relatively safe drug, however, its cost should be

	considered. Hence, routine use of the drug is not recommended. ● There are 26 ongoing trials pertaining to the efficacy and safety of remdesivir for the treatment of COVID-19. *Source:* Cabaluna, I.T., Burog, A.D., Bayona, H.G. (19 February 2021) Should Remdesivir be used for the treatment of hospitalized COVID-19 patients? National Institutes of Health, UP Manila.
Tocilizumab	*Summary of Evidence* ● Nine randomized controlled clinical trials (RCTs) (n=6,405) that evaluated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo and/or standard of care were found. ● Low to moderate quality evidence shows that tocilizumab has a beneficial effect in hospitalized COVID-19 patients on clinical improvement [rate ratio: 1.06 (95% CI: 1.00 to 1.13)], mortality reduction [rate ratio: 0.89 (95% CI: 0.82 to 0.97)], and initiation of mechanical ventilation [rate ratio: 0.78 (95% CI: 0.68 to 0.90)]. *Recommendations* ● We recommend the addition of tocilizumab to systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) and with elevated markers of inflammation (CRP > 75 mg/L). ○ Quality of evidence: Moderate ○ Strength of recommendation: Strong ● We recommend against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. ○ Quality of evidence: Very low ○ Strength of recommendation: Strong *Consensus issues* ● The high cost and limited availability of tocilizumab should be considered in our local setting. ● The potential indiscriminate use, potential adverse effects (i.e., leukemia, TB reactivation), and lack of evidence of tocilizumab on COVID-19 patients who do not require oxygenation were additional factors considered by the panel in strongly recommending against the use of tocilizumab in patients not requiring oxygen Source: Cabaluna, I. T., Garcia, A., & Bayona, H. H. G. (19 February 2021). *Evidence summary: Should tocilizumab be used for the treatment of hospitalized patients with COVID-19?* National Institutes of Health, UP Manila.

Baricitinib	*Summary of Evidence* ● One multinational double-blind placebo controlled randomized trial found that baricitinib with remdesivir showed benefit in terms of shortening time to recovery by 1 day on average [rate ratio: 1.16, (95% CI: 1.01 to 1.32)] and reducing the incidence of new mechanical ventilation or ECMO [rate ratio: 0.66 (95% CI 0.46 to 0.93)]. ● No significant effect on mortality [hazard ratio: 0.65 (95% CI: 0.39 to 1.09)] was noted and significantly fewer serious adverse events [relative risk: 0.76 (95% CI: 0.59 to 0.99)] were documented with the group treated with baricitinib and remdesivir. However, the incidence of infections was increased in patients who were taking concomitant glucocorticoids for indications other than COVID-19 [not specified in the original randomized controlled trial on which treatment arm this was observed]. ● There were no other trials found on the use of baricitinib alone or in combination with other drugs (i.e., glucocorticoids) for COVID-19. *Recommendation* We suggest the use of baricitinib in combination with remdesivir in hospitalized COVID-19 patients requiring oxygen supplementation and who cannot take corticosteroids ● Level of evidence: Low ● Strength of recommendation: Conditional There is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. ● Level of evidence: Very low There is no evidence to recommend the use of baricitinib alone in hospitalized COVID-19 patients. *Consensus issues* ● These recommendations are made in the context that dexamethasone is being considered as a standard of care for COVID-19. The incremental benefit of giving baricitinib and remdesivir with dexamethasone remains to be a research gap. Thus, there is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. ● Caution must be exercised in administering baricitinib in patients who are already taking steroids due to the likelihood of the occurrence of immunosuppression. ● Results showed that patients who received glucocorticoids had a higher risk of having serious or non-serious infections than those who did not. However, it was not specified in the RCT if these patients belonged to the treatment or control group. ● Baricitinib is being used in current local practice to replace tocilizumab in regimens with both remdesivir and dexamethasone, due to supply problems faced in the more recent months.

	• Baricitinib is approved for use in rheumatoid arthritis, and current use in COVID-19 is off-label use. Baricitinib in combination with remdesivir can be used in patients with severe COVID-19, to possibly prevent progression to critical disease. Source: Cabaluna, I.T., Burog, I., & Bayona, H.H.G. (10 April 2021). *Evidence summary: Should baricitinib with or without remdesivir be used in the management of hospitalized patients with COVID-19?* National Institutes of Health, UP Manila.
Favipiravir	*Summary of Evidence* • Six (6) randomized controlled trials were found on the use of favipiravir among patients with COVID-19. All 6 studies had some concerns in terms of risk of bias, but none of them had high risk of bias in any of the appraisal criteria. The overall quality of evidence was downgraded due to inconsistencies in combining the studies in some of the outcomes, limited sample size, and risk of bias. • Pooled results of three studies monitoring clinical improvement on day 7 showed a modest effect [relative risk: 1.58 (95% CI: 1.15 to 2.16)] favoring favipiravir compared to standard care, however, clinical improvement on day 28 showed no clinical significance [relative risk: 1.02 (95% CI: 0.95 to 1.09)]. • Incidence of viral negative conversion was not significantly different between favipiravir and standard of care on day 3 [relative risk: 1.22 (95% CI: 0.99 to 1.50)] as well as on day 7 [(relative risk: 1.10 (95% CI: 0.96 to 1.27)]. However, time to negative conversion showed a minimal advantage towards favipiravir compared to standard care [hazard ratio: 1.32 (95% CI: 1.03 to 1.69)]. • Pooled results on the incidence of adverse events (i.e., hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, to cardiac effects like bradycardia and chest pain) showed no significant difference between favipiravir and standard care [relative risk: 1.54 (95% CI: 0.87 to 2.75)]. • There were also very few or no events observed in the studies for clinically relevant outcomes such as death, respiratory distress or failure, and mechanical ventilation to make a recommendation for or against the use of favipiravir. *Recommendation* There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19, unless in the context of a clinical trial. (Very low quality of evidence) *Consensus issues* Given that there are on-going clinical trials on favipiravir, the recommendation explicitly stated that there was no recommendation on the use of favipiravir unless it will be used for clinical trials. In addition, there

	may be some implications with regard to possible reimbursements and will encourage patients to join the clinical trial. Source: Sulit, M.V.V., Garcia, A.G., & Bayona, H.H.G. (8 March 2021). *Evidence summary: Should favipiravir be used as treatment for COVID-19?* National Institute of Health, UP Manila.