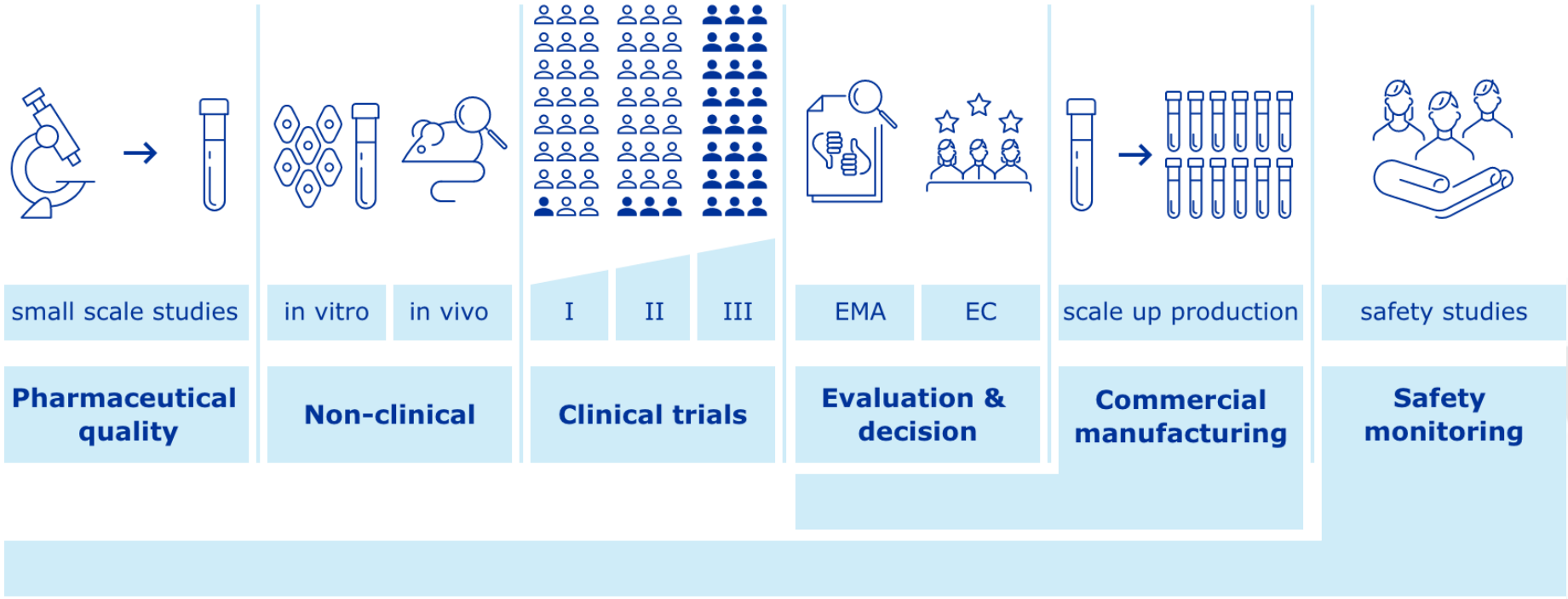
Post-Licensure Paxlovid Safety

Post-Licensing Directorate

17/02/2022

Background
Medicinal products: development, evaluation, approval and monitoring



- Prior to marketing pre-clinical and clinical safety studies characterise the safety profile of the medicinal product in the proposed indications.
- In Europe, drugs may only be approved and used if they comply with all the requirements of quality, safety and efficacy set out in the EU pharmaceutical legislation.

Background
Medicinal Product Pharmacovigilance Plan

- All medicines have risks and benefits. For a medicinal product to be authorised for use in the EU, the benefits of treatment need to outweigh the risks within the intended population.
- Not all adverse reactions can be established before a medicinal product is marketed. Hence the need for Post-Licensure Safety Monitoring and Pharmacovigilance.
- The safety of authorised medicinal products, may be further characterised via a pharmacovigilance plan to monitor the use of this product in real life patients.

Routine Pharmacovigilance Activities

Product Information	ADR reporting & Signal Management	Risk Management Plan	Periodic Safety Update Reports
• SmPC & PIL describe indications, contraindications, warnings, precautions, adverse events, drug interactions and give advice on storage, administration and correct use of medicinal product	• Systems are in place to capture spontaneous reporting from patients and HCP • Data Capture Aids for certain adverse events • Literature Monitoring • Aggregate review of cases to detect statistically disproportionately reported product-adverse event pairs	• Describes the medicinal product's safety profile [Identified Risks / Potential Risks / Missing Information] • Describes how risks may be prevented or minimised in patients • Outlines plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicinal product • Describe measuring the effectiveness of risk-minimisation measures	• Pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product • The are submitted to Health Authority by marketing authorisation holders at defined time points during the post-authorisation phase

Additional Pharmacovigilance Activities and Post-Authorisation Obligations

MALTA MEDICINES AUTHORITY

Some Examples

Educational Material and Patient Cards (aRMMs)

- Patient Reminder cards which guide patients on the use of medicinal product or advise them on the correct use of the medicinal product or how to take their medication
- Posters with step-by-step instruction for drug storage, dose planning and preparation, and administration

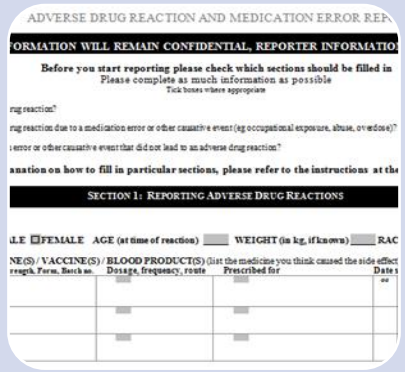
COVID-19 vaccines local monitoring

- Interval and cumulative number of reports
- Summary of designated medical events (DMEs) and Adverse Events of Special interest (AESI)
- Exposure data (age-stratified)
- Observed vs Expected Analysis
- Ongoing and closed signals in the interval
- Fatal reports (numbers and relevant cases)
- Risk/benefit considerations

Post Authorisation Safety Studies

- To identify, characterise or quantify a safety hazard
- To confirm the long safety profile of a medicinal product
- To measure the effectiveness of risk-management measures
- Can be clinical trials or non-interventional studies
- Can be imposed or voluntary

The EU system of adverse drug reactions monitoring



Spontaneous Reports (from HCPs and Consumers)

Reported to

NCAs or MAHs

Transmitted to

EudraVigilance (EU-wide database of ADR reports)

Signals Raised

Review by PRAC CHMP adoption Decision by EC

Results in

Regulatory Action (Update of PIL) & communication

The Malta Medicines Authority's Role in Safety Monitoring

The MMA monitors the safety of vaccines and medicinal products in Malta and supports the safe and rational use of medicines through the provision of objective and unbiased information.

Key activities

- Managing ADRs (Acknowledgement / Validation / Causality / Databasing / Transmission to EV)
- Raise potential safety signals to the PRAC
- Participate in EU Decision Making on Regulatory Actions at the level of the EMA
- Communicate on Safety Issues (via DHPCs and Safety Circulars)
- Approve Risk Minimisation Measures and ensure their implementation

Paxlovid

Paxlovid is a Prescription Only Medicine (POM) used for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.

Prescribers and Patients must always consult the most recent product information when using this product. Product information is subject to be updated (when required).

Further information on this product may be obtained here.

Paxlovid

Paxlovid is PF-07321332 tablets co-packaged with ritonavir tablets.

- PF-07321332 (also known as nirmatrelvir) is a SARS-CoV-2 main protease inhibitor that works by halting replication of Covid-19 virus.
- Ritonavir is an antiviral, that acts as a CYP3A inhibitor, and slows down PF-07321332's breakdown to help it remain in the body for a longer period at higher concentrations.

Paxlovid

PF-07321332 needs to be co-administered with ritonavir.

Paxlovid is administered as three tablets (2 tablets of PF-07321332 and 1 tablet of ritonavir) per dose.

Paxlovid treatment should be initiated by a treating physician within 5 days of symptom onset of COVID-19.

It is administered orally twice daily, with or without food.

Paxlovid immediate packaging

Paxlovid – Contra-indications

If you are allergic to the active ingredients (PF-07321332 or ritonavir) or any other components.

Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions.

Co-administration with potent CYP3A inducers where significantly reduced PF-07321332 or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

See section 4.3 of Paxlovid Summary of Product Characteristics (SmPC) for a guide on the medicinal products which are contraindicated with Paxlovid.

Paxlovid – Drug - Drug Interactions

- Paxlovid has significant and complex drug-drug interaction potential, primarily due to the ritonavir component of the combination.
- Before prescribing Paxlovid, prescriber should carefully review concomitant medications, including over-the-counter medicines and herbal supplements, to evaluate the potential for drug-drug interactions.
- Paxlovid cannot be started immediately after discontinuing medicinal products which are contra-indication for concomitant use with it because the effects of those medications may remain after discontinuation.
- Section 4.5 of the Paxlovid SmPC provides a guide (**not a complete list**) as to which drugs should not be taken concomitantly with Paxlovid.

Paxlovid – Drug - Drug Interactions
(some examples)

SmPC – Paxlovid (17/02/2022)

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
Antidepressants	↑Amitriptyline, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Sertraline	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).
	↑Desipramine (145%, 22%)	The AUC and C_{max} of the 2-hydroxy metabolite were decreased 15% and 67%, respectively. Dosage reduction of desipramine is recommended when coadministered with ritonavir.
Anti-gout	↑Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with Paxlovid is contraindicated (see section 4.3).

Paxlovid – Drug - Drug Interactions
(some examples)

SmPC – Paxlovid (17/02/2022)

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
	↑Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.
	↑Prednisolone (28%, 9%)	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37% and 28% after 4 and 14 days ritonavir, respectively.
Thyroid hormone replacement therapy	Levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.

Abbreviations: ATL=alanine aminotransferase; AUC=area under the curve.

Paxlovid – Drug - Drug Interactions
(some examples)

SmPC – Paxlovid (17/02/2022)

HMG Co-A reductase inhibitors	↑Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated (see section 4.3). Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir coadministration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Paxlovid – Adverse events

Tabulated summary of adverse reactions

The adverse reactions in Table 2 are listed below 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 with Paxlovid

System organ class	Frequency category	Adverse reactions
Nervous system disorders	Common	Dysgeusia, headache
Gastrointestinal disorders	Common	Diarrhoea, vomiting

SmPC – Paxlovid (17/02/2022)

Paxlovid – Special patient populations

Paxlovid is not recommended in patients with severe kidney or severe liver impairment.

The use of Paxlovid in patients with uncontrolled or undiagnosed HIV-1 infection may lead to HIV-1 drug resistance to HIV protease inhibitors.

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir. Ritonavir should be used with caution when giving Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

ADR reporting

How to report Adverse Drug Reactions (Side effects) in Malta

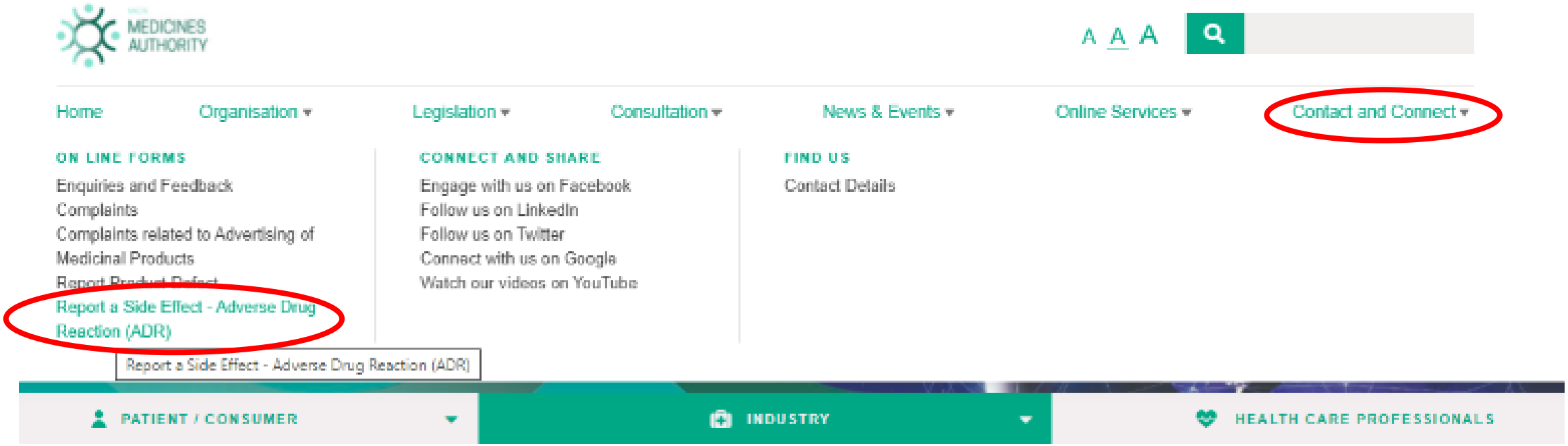
17/02/2022

How to report adverse drug reactions to the Medicines Authority

Where can I find the ADR Form for HCPs?

HCPs should use MMA ADR Paper Form
(online webportal is for patients)

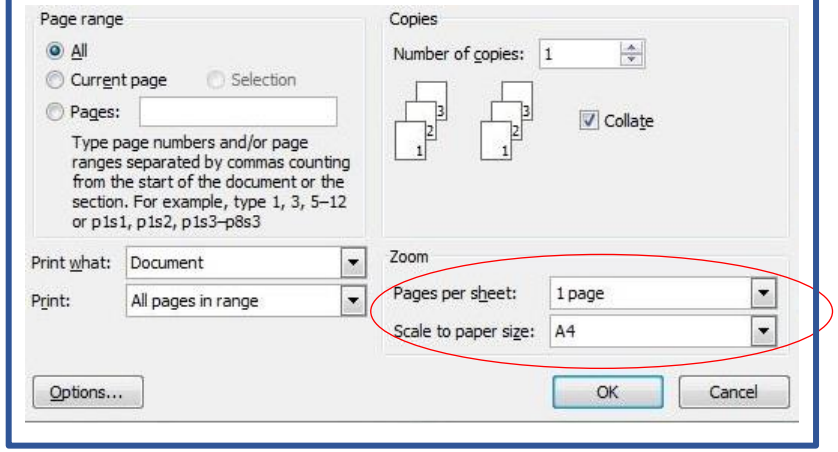
Accessible from Homepage > Contact and Connect > Online forms > Report a Side Effect



The form is downloadable from the MMA website

A Note on Printing

Print to Scale A4



If difficulties are encountered, contact the MMA. Self-addressed paper Forms can be supplied

Home / Adverse Drug Reaction

Adverse Drug Reaction

Useful Links

- Pharmacy Roster
- eHealth
- Government of Malta
- Heads of Medicines Agency
- Innovative Medicines Initiative
- European Medicines Agency

Activities

In Malta, both patients and consumers as well as healthcare professionals (HCPs) can report side effects that are experienced while taking a medicine.

For HCPs; The Adverse Drug Reactions (ADR) reporting form (for use by Healthcare Professionals) is avialable **here**

Ways HCPs can report: HCPs may fill in the ADR form electronically using MS Word and send via email to **postlicensing.medicinesauthority@gov.mt**

OR

HCPs may fill in the ADR form in ink, scan and then send via email to **postlicensing.medicinesauthority@gov.mt**

OR

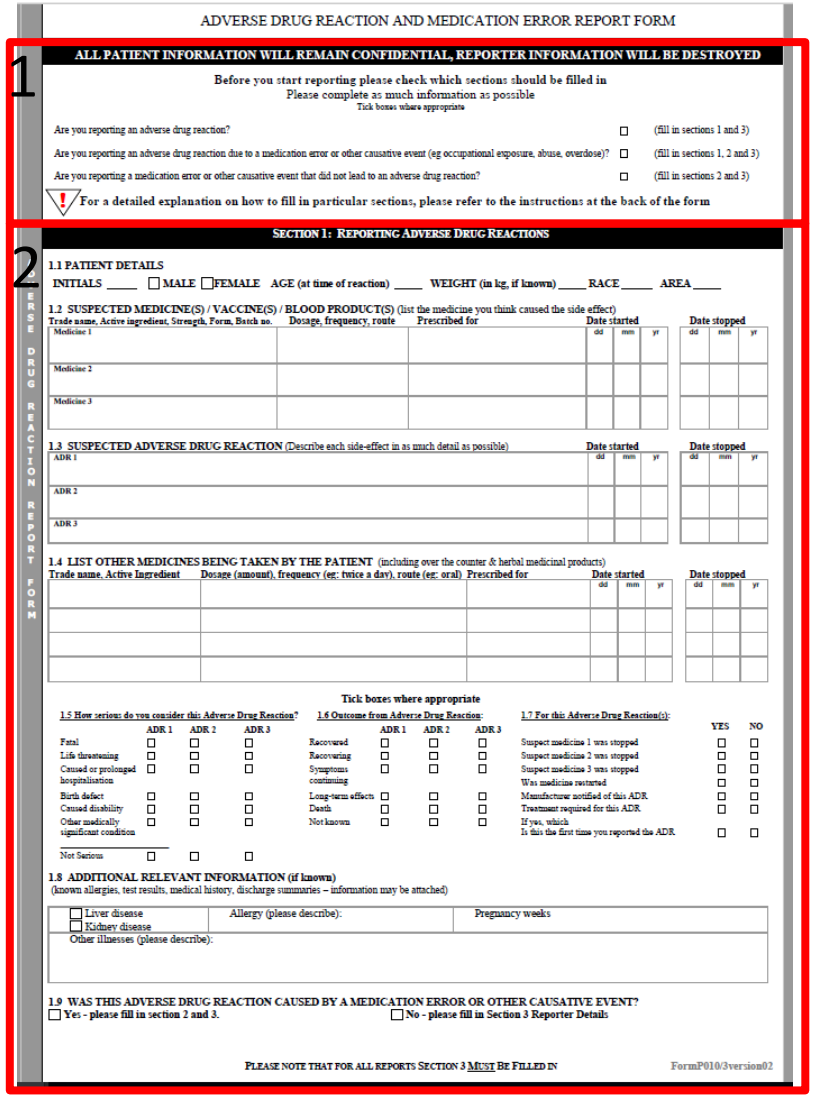
HCPs can send the ADRs to the Marketing Authorisation Holder on the address that can be found on the medicine's package(in such cases do not send the same report to the Medicines Authority to avoid creation of dublicate reports).

For Patient and consumers; Patients and consumers should use the **online side effect report form** which is sent directly to the Medicines Authority

Understanding the reporting form

Main Sections

- Decision Tree (1)
- Section 1: Reporting Adverse Drug Reactions (2)
- Section 2: Medication Error Reporting (3)
- Section 3: Reporter Details (4)
- Instruction Sheet Overleaf



ADVERSE DRUG REACTION AND MEDICATION ERROR REPORT FORM

1

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in
Please complete as much information as possible
Tick boxes where appropriate

Are you reporting an adverse drug reaction? ☐ (fill in sections 1 and 3)

Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)? ☐ (fill in sections 1, 2 and 3)

Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction? ☐ (fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

2

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

ADVERSE DRUG REACTION REPORT FORM

1.1 PATIENT DETAILS

INITIALS ____ ☐ MALE ☐ FEMALE AGE (at time of reaction) ____ WEIGHT (in kg, if known) ____ RACE ____ AREA ____

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) (list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started dd mm yr	Date stopped dd mm yr
Medicine 1				
Medicine 2				
Medicine 3				

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side-effect in as much detail as possible)

	Date started dd mm yr	Date stopped dd mm yr
ADR 1		
ADR 2		
ADR 3		

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started dd mm yr	Date stopped dd mm yr

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalization	☐	☐	☐
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☐	☐	☐
Not Serious	☐	☐	☐

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☐	☐	☐
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☐	☐	☐

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☐
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☐	☐
If yes, which Is this the first time you reported the ADR	☐	☐

1.8 ADDITIONAL RELEVANT INFORMATION (if known)
(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe):	Pregnancy weeks
Other illnesses (please describe):		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?
☐ Yes - please fill in section 2 and 3. ☐ No - please fill in Section 3 Reporter Details

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

FormP010/3version02

3

SECTION 2: MEDICATION ERROR REPORTING

MEDICATION ERROR REPORT FORM

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
	If the same details were filled in section 1.2, you can leave this section blank		
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg: blister pack, loose strip or other)			

2.2 DATE OF EVENT
Date event occurred: ___/___/___ Date event was detected: ___/___/___

2.3 DESCRIBE THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE) RELATED TO THE MEDICINE

Free Text (eg: Wrong route; wrong dose; wrong medicine; other):	For medication errors – tick the stage the error may have occurred
	Prescribing ☐
	Dispensing ☐
	Preparation ☐
	Storage ☐
	Distribution ☐
	Administration ☐

2.4 LOCATION WHERE THE EVENT OCCURED
(eg: Nursing home, Home, Hospital, Pharmacy, Clinic, Other)

2.5 SUSPECTED CAUSE OF THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RELATED TO THE MEDICINE

2.6 ANY FACTORS CONTRIBUTING TO THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RELATED TO THE MEDICINE
(eg: Omission of meals, concomitant alcohol intake, over exposure to heat and sun, other)

2.7 WAS THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT PREVENTABLE? ☐ Yes ☐ No

2.8 WAS ANY REMEDIAL ACTION RELATED TO THE MEDICINE TAKEN?
☐ Yes (please describe) ☐ No

2.9 RECOMMENDATIONS TO PREVENT REPEAT INCIDENT

2.10 DID THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RESULT IN AN ADVERSE DRUG REACTION?
☐ Yes - please fill in section 1. ☐ No - please fill in your details below

4

SECTION 3: REPORTER DETAILS
Details will be destroyed following transmission to the EU central side effect database Eudravigilance

Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient
Name:
Address:
Telephone/Mobile:
E-mail address:

Signature _____ Date _____

The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health

☐ SUPPLY OF ADR REPORT CARDS IS REQUIRED
☐ INFORMATION ABOUT OTHER ADRs IS REQUIRED

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

FormP010/3version02

Adverse Event reporting by Healthcare professionals

To the MMA directly

PRINT, FILL IN AND SEND BY POST TO

Medicines Authority
Sir Temi Żammit Buildings,
Malta Life Sciences Park,
San Ġwann SĠN 3000
Malta

OR

FILL IN WORD AND EMAIL TO FILL IN INK, SCAN AND EMAIL TO

postlicensing.medicinesauthority@gov.mt

OR

To the MAH

SEND TO THE MARKETING AUTHORISATION HOLDER OF THAT PRODUCT

Do Not send the same reports to the MAH and to the Medicines Authority

Capturing Good Quality ADR Data

Please report all suspected adverse drug reactions for Paxlovid and other medicinal products / vaccines

Include as much information as possible. Additional information (e.g Lab tests, pictures etc..) can be attached to the ADR form

Any follow-up information for a report that has already been reported may be sent to the Medicines Authority in another form or through other reporting channels. **Please indicate this as follow up report**

All dates should as specific as possible "dd/mm/yyyy"

Hallmarks of a good quality report
Batch/Lot number
ADR start/stop date
Suspect drug start/stop date
Indication of suspected drug
Patient outcome and seriousness
Rechallenge and Dechallenge
Patient details • Past medical history • Concomitant drugs

Additional Resources for HCPs

- HCPs may refer to the Adverse Drug Reaction Reporting & Pharmacovigilance Guidance Notes for Healthcare Professionals for further background and instruction on how to report ADRs.
- The ADR form for HCPs also contains a detailed step by step instruction sheet overleaf.

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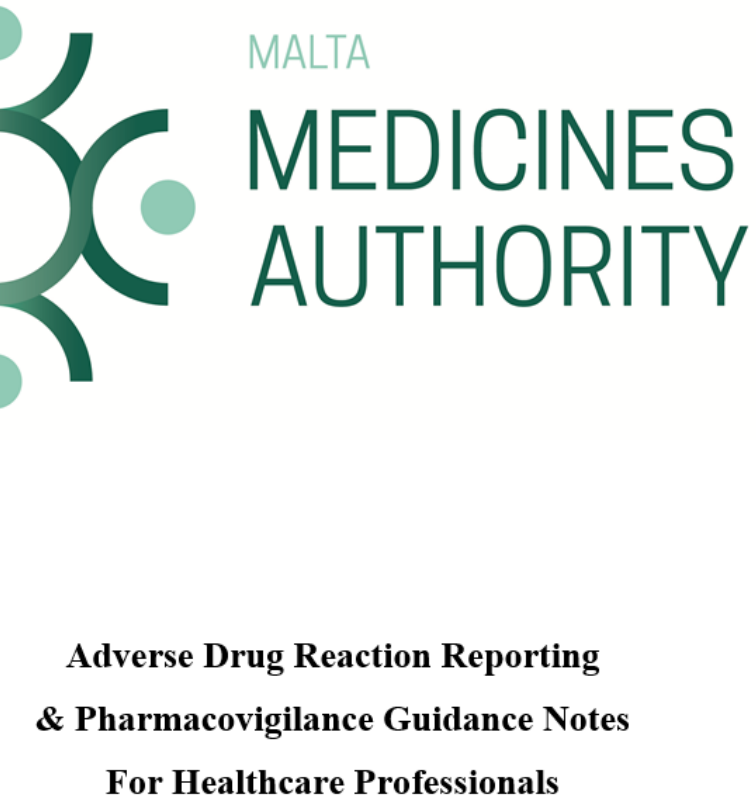
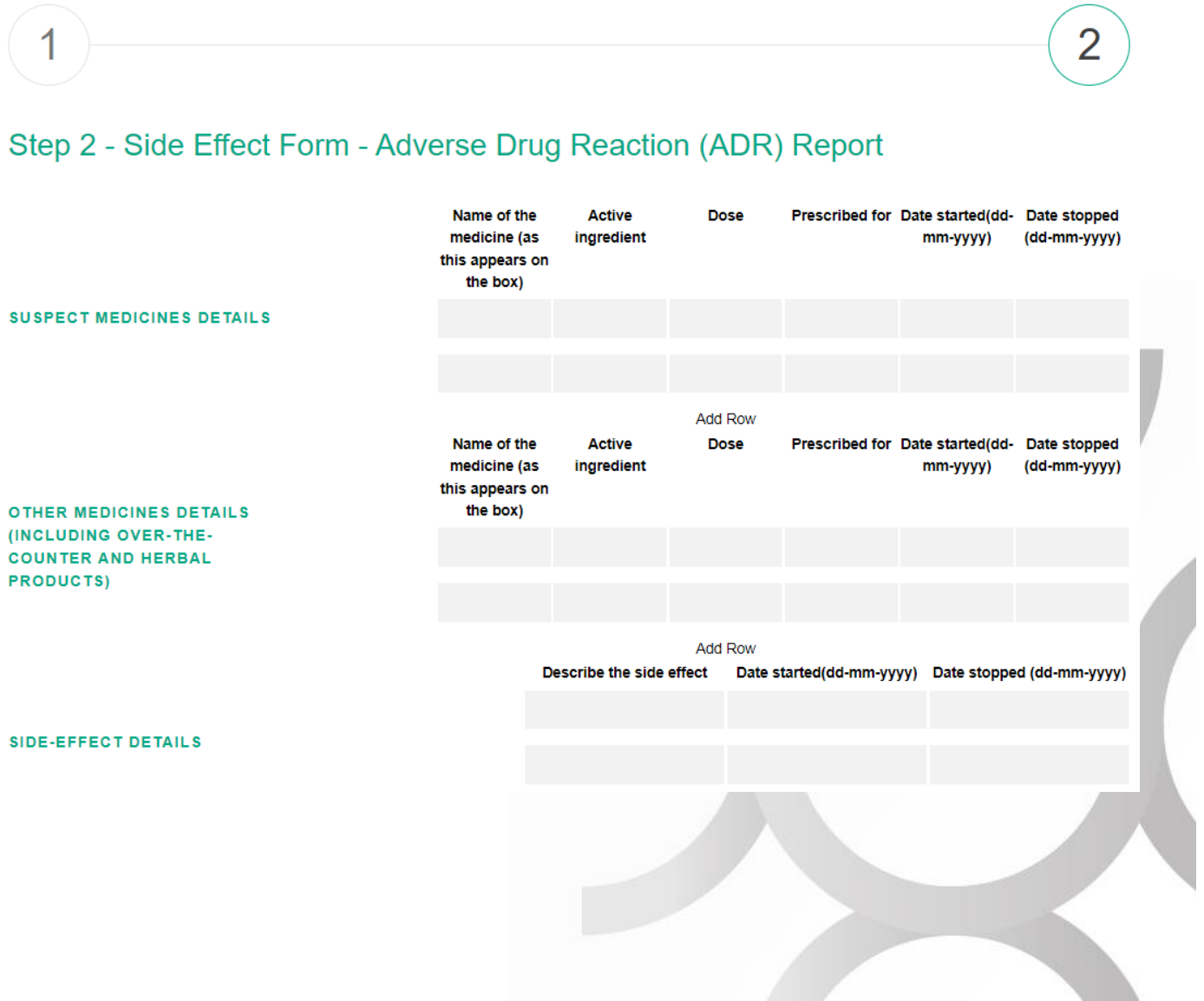


Adverse Event reporting by patients

In Malta, patients and consumers may report side effects directly to the Medicines Authority by using the online reporting form which can be found here.



Conclusion

- Refer to the Paxlovid SmPC.
- Consider the potential for drug interactions prior to and during Paxlovid therapy and review concomitant medications during Paxlovid therapy.
- Consider special patient populations prior to and during Paxlovid therapy.
- In the EU there is robust system for safety monitoring of medicinal products.
- Reporting makes medicines safer to use.
- Anyone can contribute to Pharmacovigilance and ultimately patient safety.

Thank You For Your Attention

HCP queries can be sent to: postlicensing.medicinesauthority@gov.mt