Germline BRCA1 and BRCA2 Testing in Patients with Early Stage Breast Cancer Eligible to Receive Olaparib Guidance

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Objective and Scope

The aim of this document is to provide clinical staff with guidance on the germline BRCA1 and BRCA2 (gBRCA1/gBRCA2) gene testing pathway for patients with early stage breast cancer who are potentially eligible for olaparib. The guidance is relevant to all staff involved with the management of patients with early breast cancer. For those patients where a germline BRCA1 and BRCA2 alteration is subsequently identified and who are eligible to receive olaparib, this guideline summarises the prescribing information and recommended baseline investigations and on-treatment monitoring requirements.

Section 1: Germline BRCA1 and BRCA2 testing

Background to clinical need for testing

Olaparib (alone or with endocrine therapy) is recommended by NICE within its marketing authorisation, as an option for the adjuvant treatment of HER2-negative high-risk early breast cancer that has been treated with neoadjuvant or adjuvant chemotherapy in adults with germline *BRCA1* or *BRCA* 2 mutations (1).

The clinical evidence to support this comes from OlympiA, a randomised double-blind placebo-controlled trial (n=1,836) (2,3). The trial compared olaparib with placebo in people with (germline) *BRCA* mutation-positive HER2-negative high-risk early breast cancer. People in the trial had either had neoadjuvant or adjuvant treatment at the point of randomisation.

The definition of high risk is reflected in the eligibility criteria for the drug.

With a median follow-up of 3.5 years, the second interim analysis of overall survival (OS) demonstrated significant improvement in the olaparib group relative to the placebo group [hazard ratio 0.68; 98.5% confidence interval (CI) 0.47-0.97; P = 0.009]. Four-year OS was 89.8% in the olaparib group and 86.4% in the placebo group (Δ 3.4%, 95% CI -0.1% to 6.8%). Four-year invasive disease free survival (IDFS) for the olaparib group versus placebo group was 82.7% versus 75.4% (Δ 7.3%, 95% CI 3.0% to 11.5%) and 4-year distant disease free survival (DDFS) was 86.5% versus 79.1% (Δ 7.4%, 95% CI 3.6% to 11.3%), respectively.

Cancer predisposition gene testing based eligibility for PARP inhibitor (R444.1 criteria)

The testing criteria for adjuvant olaparib match those in indication R444.1 in version 7.2 of the National genomic test directory for cancer (4).

The criteria are summarized in Figure 1 below.

Germline *BRCA1* and *BRCA2* based on R444.1 criteria will be performed as part of the NHSE germline gene R444.1/R208 panel, which also includes *PALB2, RAD51C, RAD51D, ATM,* and *CHEK2.*

Figure 1: Testing criteria for NICE approved PARP inhibitor treatment for early breast cancer (R444.1)

For people with triple negative breast cancer who have received neo-adjuvant chemotherapy:

- residual invasive cancer in the breast, the resected lymph nodes (non-pathological complete response) or both at the time of surgery

For people with triple-negative breast cancer having adjuvant chemotherapy:

- node-positive OR
- node-negative cancer with a primary tumour ≥ 2 cm

For people with hormone receptor-positive, HER2-negative breast cancer who have received neoadjuvant chemotherapy:

- residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery, AND a CPS + EG score of ≥3 based on pretreatment clinical and post treatment pathological stage, receptor status and histological grade

For people with hormone receptor-positive, HER2-negative breast cancer having adjuvant chemotherapy:

- 4 or more pathologically confirmed positive lymph nodes.

The CPS&EG scoring system is made up as follows to a maximum score of 6:

- Clinical stage: 0 for stage 0-IIA, 1 for stages IIB and IIIA, 2 for stages IIIB and IIIC (AJCC staging)
- Pathological stage: 0 for stages 0 and I, 1 for stages IIA-IIIB, 2 for stage IIIC (AJCC staging)
- Receptor status: 0 for ER positive, 1 for ER negative

- Nuclear grade (Bloom and Richardson expected but if not available use regular histological grade): 0 for nuclear grade 1-2, 1 for nuclear grade 3

Cancer predisposition gene testing based on personal and family history (R208 criteria)

Oncology/surgical oncology healthcare professionals with appropriate training and experience can directly request the NHSE germline gene R444.1/R208 panel (BRAC1, BRCA2, PALB2, RAD51C, RAD51D, ATM and CHEK2) if the following criteria are met:

- Triple negative breast cancer, under the age of 60; or
- Breast cancer diagnosed under 40; or
- Male breast cancer.

These criteria form part of the National genomic test directory criteria R208.

Referral to cancer genetics based on personal and family history of cancer

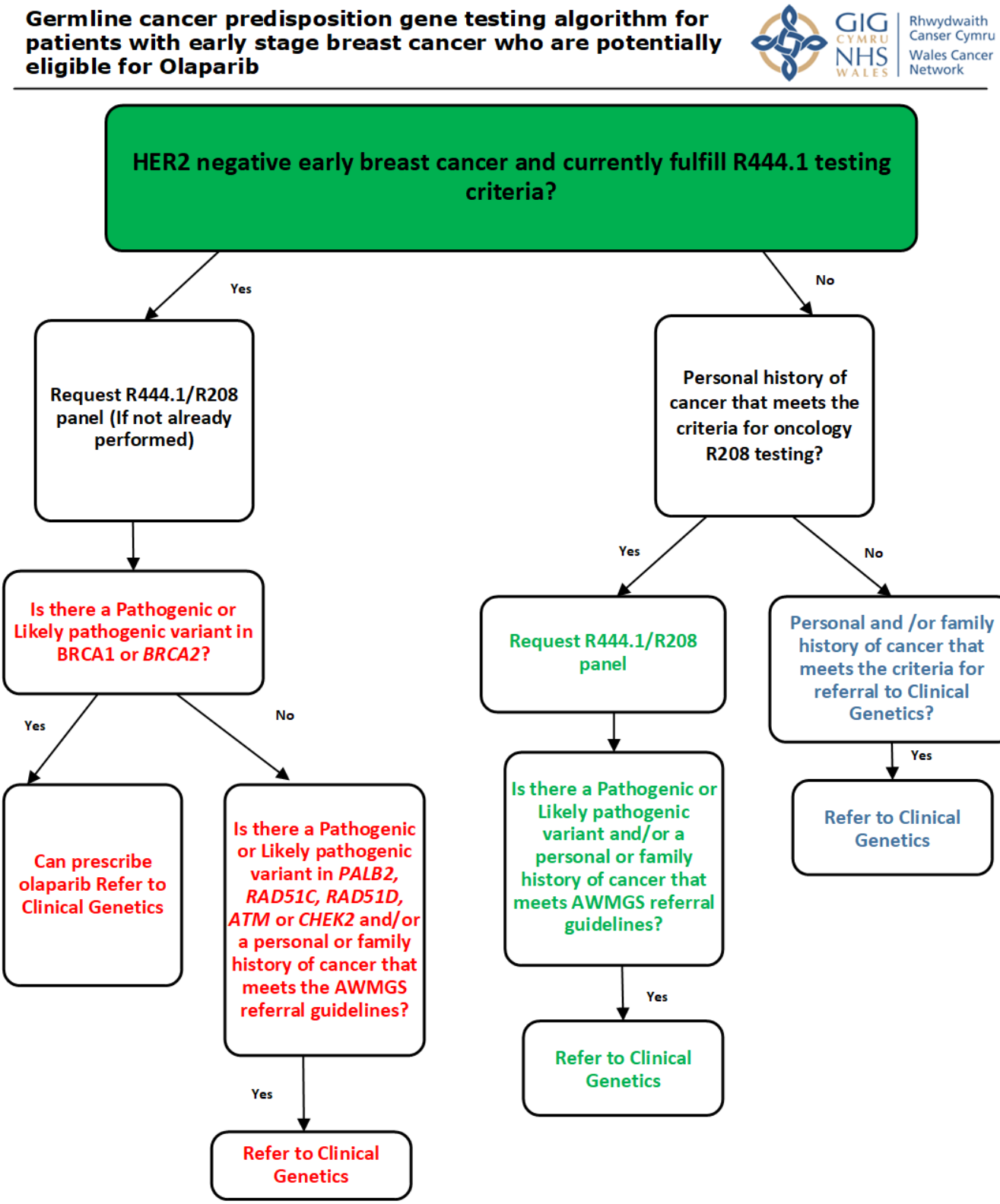
Patients with a personal history of breast cancer can be referred to the AWMGS if one or more of the following criteria are met:

1. Individual with cancer:
    - Breast cancer age < 40 years; or
    - Male breast cancer (any age); or
    - Bilateral breast cancer (any age); or
    - Breast AND ovarian cancer (any age)

2. Individual with breast or ovarian at any age and 1 first degree relative (FDR)* (male or female) with:
    - Breast cancer (any age); or
    - Ovarian cancer (any age); or
    - Second degree relative (SDR) - if the intervening relative is male

3. Individual with breast or ovarian at any age and 2 or more FDR or SDR relatives (same side of family) with:
    - Breast and/or ovarian cancer at any age

Germline gene testing algorithm



Breast Oncology genomic NHSE germline gene R444.1/R208 panel request process

Germline cancer predisposition gene testing is performed by the All Wales Medical Genomics Service (AWMGS)

All samples for R444.1 or R208 testing should be accompanied Breast Oncology genomic request form (NHSE germline gene panel R444/R208)

The request form can be downloaded from the AWMGS website.

Please tick all reasons for testing that apply.

Current guidance recommends germline testing requires patient consent. It is the responsibility of the clinician requesting the test to obtain this and it is assumed that this has been done if a sample is sent to the laboratory (5).

A recommended consent form to record written consent for germline testing is available from the AWMGS website.

A minimum of 5ml of blood is required to be collected in an EDTA tube.

The current turnaround time for testing is 6 weeks.

Expedited testing for olaparib eligibility is available. Please ONLY request expedited testing if a 6 week turnaround time would lead to unacceptable delays in starting olaparib. Processing of expedited test requests will be prioritised, where possible, with a target turnaround time of 3 weeks.

Unwarranted requests for expedited testing may lead to delays in the standard turnaround time.

All Wales Medical Genomics Service contact details

All Wales Genetics Laboratory

Institute of Medical Genetics

University Hospital of Wales

Heath Park

Cardiff

CF14 4XW.

Telephone: 02921845347

Email address: Admin.Genetics.cav@wales.nhs.uk

Website: http://www.medicalgenomicswales.co.uk

Opening hours: Monday – Friday 8.30am – 5:00pm

Timing of germline testing based on R444.1 criteria

Germline testing based on R444.1 testing criteria should be requested at the earliest stage, either after primary surgery or after neoadjuvant chemotherapy.

Timing of germline testing based on R208 criteria

Germline testing based on R208 testing criteria should be requested as early as possible in the treatment pathway.

Interpreting test results

All reports on NHSE germline gene R444.1/R208 panel will include statements about:

- Whether any germline pathogenic or likely pathogenic variants in cancer predisposition genes were found
- Whether the patient is potentially eligible for olaparib

Patients with a germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant will potentially be eligible for olaparib.

Patients with a germline *BRCA1* or *BRCA2* variant of uncertain significance (VUS), likely benign or benign variant will not be eligible for olaparib.

Patients with a germline pathogenic or likely pathogenic variant in a cancer predisposition gene will need referral to a clinical genetics service.

Patients with a variant of uncertain significance (VUS), likely benign or benign variant will need referral to clinical genetics service if their personal and/or family history of cancer meets the AWMGS referral criteria.

References

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Part 2: Olaparib prescribing information

Mechanism of action of Olaparib

Olaparib is an immunosuppressive agent, which is a selective enzyme inhibitor of the poly (ADP-ribose) polymerase family (e.g., PARP-1, PARP-2, and PARP-3). Binding to PARP inhibits single stranded DNA base excision repair and creates PARP-DNA complexes that lead to double-stranded DNA breaks, ultimately causing cell death in tumours that cannot repair double stranded breaks reliably (e.g., tumours with homologous replication deficiency, such as those with BRCA1/2 mutation).

Eligibility criteria for treatment with Olaparib

- Germline pathogenic or likely pathogenic BRCA1 or BRCA2 mutation
- HER2 negative, ER positive or triple negative (ER/PR negative, HER2 negative) stage II-III breast cancer
- For people with triple negative breast cancer who have received neo-adjuvant chemotherapy:
    - residual invasive cancer in the breast, the resected lymph nodes (non-pathological complete response)
    - or both at the time of surgery
- For people with triple-negative breast cancer having adjuvant chemotherapy:
    - node-positive OR
    - node-negative cancer with a primary tumour ≥ 2 cm
- For people with hormone receptor-positive, HER2-negative breast cancer who have received neoadjuvant chemotherapy:
    - residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response)
    - or both at the time of surgery,
    - AND a CPS + EG score of ≥3 based on pre-treatment clinical and post treatment pathological stage, receptor status and histological grade
- For people with hormone receptor-positive, HER2-negative breast cancer having adjuvant chemotherapy:
    - 4 or more pathologically confirmed positive lymph nodes.
    - Completed definitive local therapy and 6 cycles of (neo)adjuvant systemic therapy with an anthracycline (unless contraindicated) and a taxane

- PS 0-1

Prescribing information for Olaparib

- Olaparib should be used after neo-adjuvant or adjuvant chemotherapy, either:
    - As monotherapy in triple negative early breast cancer, or
    - With endocrine treatment in hormone receptor-positive HER2-negative early breast cancer.

- The decision to commence treatment with Olaparib should be made by the treating clinician on a case-by-case basis, taking into account patient specific factors (e.g. comorbidities, acceptability of potential toxicities) and clinical experience.

- Treatment must be started 2 to 12 weeks after local therapy (including radiotherapy)

- Once commenced, it is recommended that patients are treated for up to 1 year or until disease progression, or unacceptable toxicity, or if the patient chooses to stop treatment.

Baseline investigations and on-treatment monitoring for Olaparib

Summary of the required baseline investigations and on-treatment monitoring for patients receiving olaparib treatment.

Investigations	**Timing within treatment plan**
FBC	Baseline & prior to each cycle
U&Es and LFTs	Baseline & prior to each cycle
SACT assessment to review toxicities	Baseline & prior to each cycle

Drug	Dose	Route	Frequency	Cycle length	Duration of treatment
Olaparib	300mg*	po	Twice daily	28 days (continuous)	1 year

Olaparib is available as 100 mg and 150 mg tablets

Administration of Olaparib including counselling points for patients

- Swallow whole with water (not chewed)
- Take approximately 12 hours apart with or without food
- It is recommended that patients are treated for up to 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first
- Store tablets at room temperature (2-30 degrees)
- **Missed dose:**
  - take their next normal dose at scheduled time
- **Caution:**
  - when driving or using machinery. Olaparib has a moderate influence on the ability to drive and use machines. Patients may experience fatigue, asthenia or dizziness
- **Fertility/pregnancy:**
  - Women of childbearing potential should use effective contraception while on olaparib and for at least one month following the last dose. If a patient becomes pregnant whilst on treatment, olaparib should be discontinued immediately. No adverse effects on male or female fertility were observed

in animal studies. Avoid breast-feeding during treatment and for 1 month after the last dose.

Olaparib dose modification guidance

Renal Impairment

Creatinine Clearance (ml/min)	**Dose**
>50ml/min	No dose adjustment
31-50ml/min	200mg twice daily
≤30ml/min or haemodialysis	Not recommended as safety and pharmacokinetics have not been studied in these patients. Only use these patients if the benefits outweigh the potential risk, and the patient should be carefully monitored for renal function and adverse events.

Hepatic impairment

Child-Pugh Score	**Dose**
A or B - Mild to moderate	No dose adjustment required
C – Severe impairment	Not recommended for use these patients as safety and pharmacokinetics have not been studied in these patients.

- *Elderly:*
  - No adjustment in starting dose is required for elderly patients.
- *Non-Caucasian patients:*
  - Limited clinical data available in these patients. However, no dose adjustment is required on the basis of ethnicity.
- *Paediatric population:*
  - No safety and efficacy data in children and adolescents.

Dose modification levels when managing toxicity (advised by manufacturer)

Dose level	Dose
Initial starting dose	300mg twice daily
1st dose reduction	250mg twice daily
2nd dose reduction	200mg twice daily
3rd dose reduction	Discontinue treatment

Interactions documented with Olaparib

Refer to Olaparib SPC for up to date interaction information using link: **https://www.medicines.org.uk/emc/product/9204/smpc**

Dose adjustments for co-administration with CYP3A inhibitors

Olaparib undergoes extensive metabolism by CYP3A4/5 and P-gp therefore inducers or inhibitors of these isoenzymes should be avoided where possible.

N.B. Caution should be taken and patients closely monitored if olaparib is used in combination with vaccines or immunosuppressant therapies, as this has not been studied

Isoenzyme inhibitors/inducers	Drug examples	Olaparib dose if must be administered
Strong CYP3A inhibitors	itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir	**Should be avoided when taking olaparib** but if no alternative available, reduce olaparib dose to 100mg twice daily when prescribed in combination and for 5 half-lives after stopping the concomitant medicine. After the washout of the inhibitor is complete, the

		olaparib dose can be re-escalated.
Moderate CYP3A inhibitors	ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	**Should be avoided when taking olaparib** but if no alternative available reduce olaparib dose to 150mg twice daily when prescribed in combination and for 3 half-lives after stopping the concomitant medicine. After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.
Strong CYP3A inducers	phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort	If the use of strong or moderate inducers is considered necessary for the patient's safety this could diminish the clinical efficacy of olaparib. If a patient requires the use of a concomitant inducer, they must be monitored carefully for any change in efficacy of olaparib.
Moderate CYP3A inducers	bosentan, efavirenz, modafinil	If the use of strong or moderate inducers is considered necessary for the patient's safety this could diminish the clinical efficacy of olaparib. If a patient requires the use of a concomitant inducer, they must be monitored carefully for any change in efficacy of olaparib.
Olaparib acting as a CPY3A inhibitor	digoxin, dabigatran, colchicine, methotrexate, rosuvastatin and sulfasalazine, glibenclamide, repaglinide, statins, and valsartan, metformin,	Increased exposure to these medicines may occur whilst on concomitant treatment. Monitor patient closely

	cyclosporin, ergot alkaloids, fentanyl, pimozide, tacrolimus and quetiapine.	
Olaparib acting as a CPY3A inducer	Hormonal based contraceptives	The efficacy of hormonal based contraceptives may be reduced due to potential olaparib CYP3A induction. Recommend additional non-hormonal contraception. Consider pregnancy tests in women of child bearing potential prior to starting olaparib, periodically during treatment, and at one month post therapy

Common adverse drug reactions reported by manufacturer (see SPC: Olaparib)

Type of ADR	ADR experienced	Common/Uncommon
Gastrointestinal disorders	Nausea, Vomiting, Diarrhoea, Dyspepsia Upper abdominal pain, Stomatitis	Very common Common
General disorders	Fatigue (including asthenia), Decreased appetite, Headache, Dizziness, taste disturbance	Very common
Haematological toxicity	Anaemia, Common - neutropenia, thrombocytopenia and leukopenia. Lymphopenia	Very common Uncommon

Rare but significant adverse drug reactions reported by manufacturer (see SPC: Olaparib)

Type of ADR	ADR experienced
Secondary myelodysplastic syndrome and acute myeloid leukemia (MS/AML)	- If patients' blood parameters remain clinically abnormal after 4 weeks of dose interruption of olaparib, bone marrow analysis is recommended. The incidence of MDS/AML in clinical trials of olaparib was <1.5% and the majority of events had a fatal outcome. - Previous treatment with cisplatin or other DNA damaging treatments (including radiotherapy), history of previous cancer or bone marrow dysplasia, and germline BRCA mutations were considered potential contributing factors.
Pneumonitis	- Reported in a small number of patients, monitor patients for new or worsening respiratory symptoms such as dyspnoea, cough and fever. If pneumonitis is confirmed, olaparib should be discontinued. - Patients with lung metastases, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy may be predisposed.

Management of common toxicities

Pneumonitis

Pneumonitis diagnosis	Advice
Suspected	Interrupt treatment and prompt investigation is necessary
Confirmed	Stop olaparib treatment and treat pneumonitis appropriately

Haematological toxicity

Haematological parameters	**Advice**
Hb ≥10g/dL & ANC ≥1.0x10^9/L, & Plt ≥100x10^9/L	Proceed with treatment
Hb <10g/dL and/or ANC ≤0.9x10^9/L* and/or Plt ≤99x10^9/L	Delay treatment for one week and once recovered, re-commence at next dose level
If Hb<8g/dL only	Interrupt treatment and consider use of blood transfusions. If recommenced treatment in less than 4 week then start at same dose, but if 4 weeks or more delay then recommence at a lower dose

No role for GCSF in primary prophylaxis to raise ANC. If prescribed when treatment delayed, ensure olaparib taken at least 24 hours before

Non- Haematological toxicity

Grade of toxicity	**Advice**
Grade 1	Continue treatment but closely monitor
Intolerable Grade 2	Withhold treatment and restart at a reduced dose when toxicity returns to grade 1 or less
Grade 3 or 4	Withhold treatment and restart at a reduced dose when toxicity returns to grade 1 or less

*****Adverse effects experienced and reported during the use of Olaparib should be reported through the Yellow Card Scheme Wales (https://yellowcard.mhra.gov.uk) *****

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