Clozapine: What GPs need to know

Clozapine

Background information

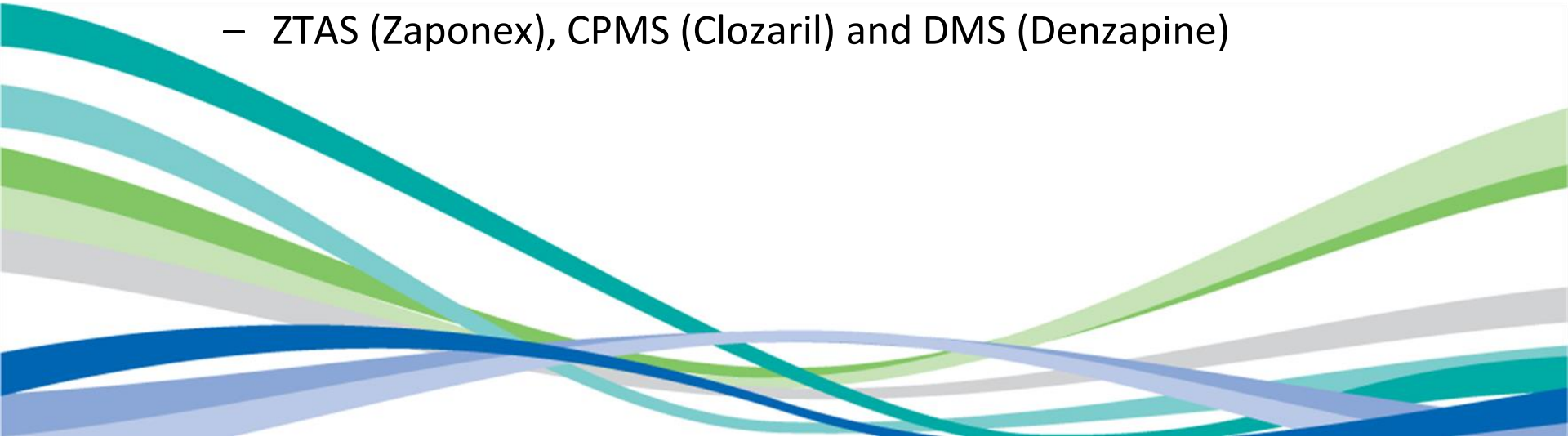
- Second generation antipsychotic
  - How does it work???
    - Low D2 receptor blocking
    - Potent anticholinergic and alpha blocking

- Licensed for
  - Treatment resistant schizophrenia
  - Psychosis in Parkinson's disease

Barnsley formulary: RED

Agranulocytosis/Neutropenia

- Unchecked, risk of sepsis, can be fatal.
  - Risk of agranulocytosis ~0.8%
  - Risk of neutropenia ~2.7%
- Patient, consultant psychiatrist and dispensing pharmacy must all be registered with the same clozapine monitoring agency.
- All patients must have mandatory regular FBC monitoring.
- Results must be submitted to the monitoring agency to authorise the on-going supply of clozapine.
  - Clozapine must be prescribed by brand
  - ZTAS (Zaponex), CPMS (Clozaril) and DMS (Denzapine)



Agranulocytosis/Neutropenia

GP responsibilities

- To be alert to complaints of flu-like symptoms or other evidence of infection this may be indicative of agranulocytosis/neutropenia.
  - Order FBC as soon as possible

Any concerns report to SWYFT

Constipation

- Common side effect, most patients will experience it at some point while on treatment.
  - Likely due to clozapine anticholinergic properties
- Constipation can occur at any time and at any dose
- Usually mild, but can vary from person to person.
- Rarely clozapine induced constipation has been associated with serious and possibly fatal complications including intestinal blockage, bowel perforation and toxic megacolon.
  - More dangerous than agranulocytosis
  - Severe constipation ~20% mortality rate.
- Be aware when initiating/increase dose of other medicines that that can cause constipation, particularly
  - Anticholinergic
  - Opioids
    - Aware changes in physical health
      - Dehydrated
      - Bed bound
      - Poorly controlled diabetes, hypothyroidism

Management

- Promote health bowel health where ever possible:
    - Eating more fibre
    - Avoid dehydration (note caffeine, alcohol and fizzy drinks)
    - Keeping active

Management: Laxatives

Acute

- Review and discuss what has previously helped.
- Urgency
- High risk patients
- Any red flags

Maintenance

- Review and discuss what has previously helped, including what helped during acute constipation.

Generally avoid bulk-forming laxatives

Red Flag

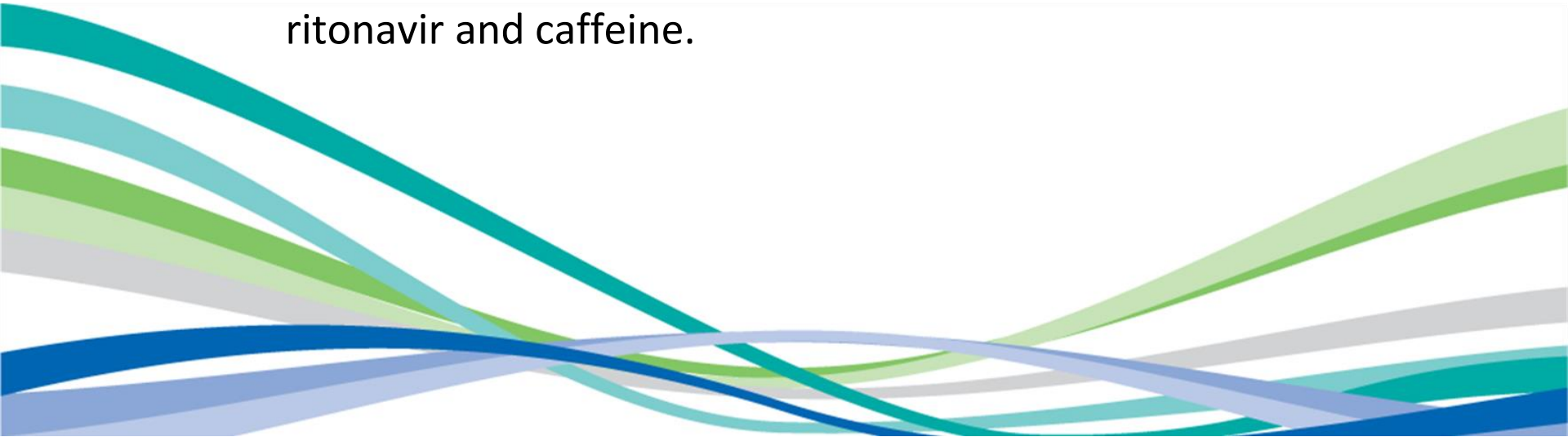
Abdominal and/or chest pain
You notice your belly is larger, swollen or distended
Nausea (maybe on and off)
Vomiting
Feel unwell/feverish
Constipation followed by explosive diarrhoea or leaking diarrhoea but still feeling constipated/discomfort (overflow)

Medical emergency refer patients to A+E

Interactions

Narrow therapeutic range

- Pharmacokinetics: metabolised predominantly by CYP^{450}1A2
  - Inducers
    - Omeprazole, rifampicin, phenytoin, carbamazapine, smoking
  - Inhibitors
    - SSRIs (fluvoxamine, fluoxetine, paroxetine, venlafaxine), ketoconazole, erythromycin, clarithromycin, ciprofloxacin, COC, ritonavir and caffeine.



Interactions

- Pharmacodynamics: dopamine D1, dopamine D2, 5-HT2A, alpha1-adrenoceptor, and muscarinic-receptor antagonist.
  - Medication with sedative or respiratory depressant effects (benzodiazepine, z-drugs, opioids)
  - Antihypertensive
  - Drugs that can prolong QTc
  - Anticholinergic drugs
  - C/I any medicines with significant risk of agranulocytosis
    - Carbamazepine, DMARDs, carbimazole, depot antipsychotics, chemotherapy etc.

Please note this is not an exhaustive list of interactions, please see the SPC

Smoking + Clozapine

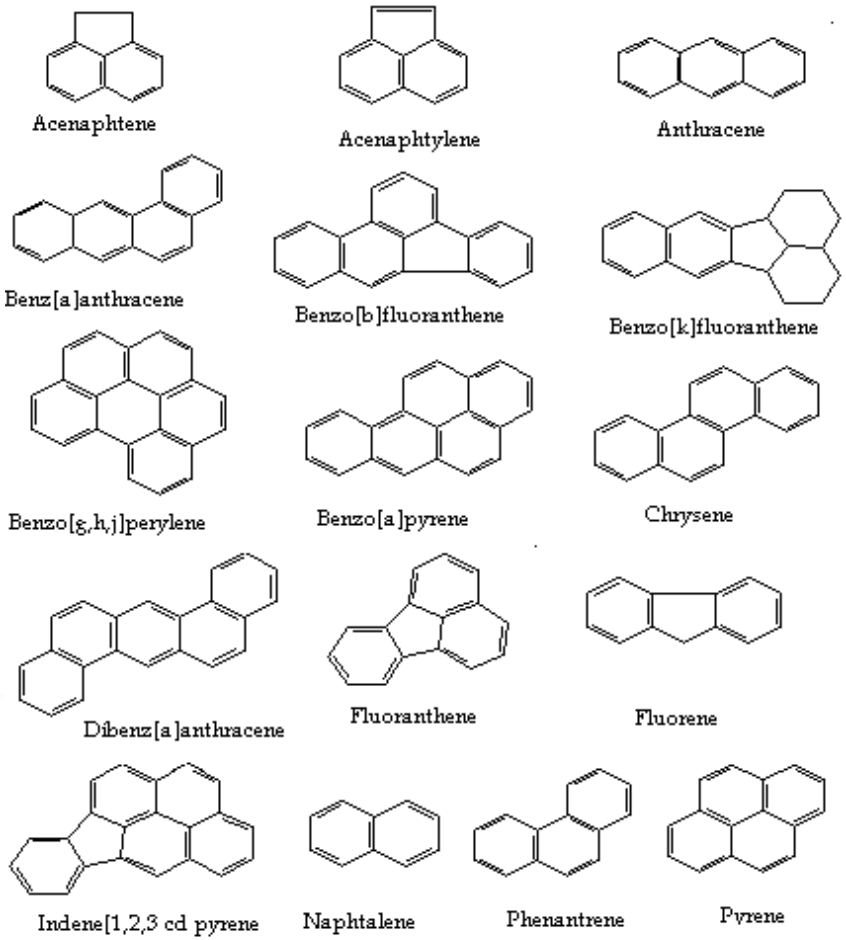
Smoking is a potent CYP^{450} 1A2 inducer

- Smoking increases the livers capability and the speed it metabolises clozapine
- Smokers generally need higher doses of clozapine than non-smokers.

Cigarette smoke is a complex mixture of chemicals.

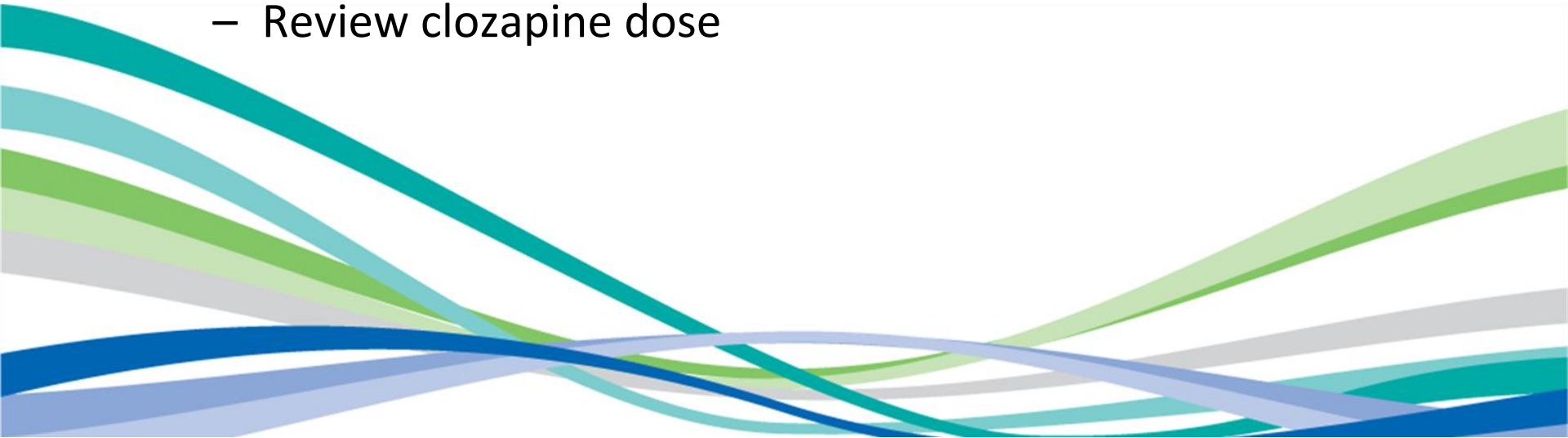
Nicotine does <u>NOT</u> interact with clozapine

PolyCyclic aromatic Hydrocarbons



- **Stop smoking**, (including switching to NRT, e-cigs/vaping or any other form of smokeless tobacco)
  - the levels of clozapine in the blood will increase (30-70% increase).
  - Risk of potentially **fatal toxicity** (seizures, respiratory depression, coma, death)
- **(Re)start smoking**, the levels of clozapine in the blood will decrease.
  - Increased risk of relapse

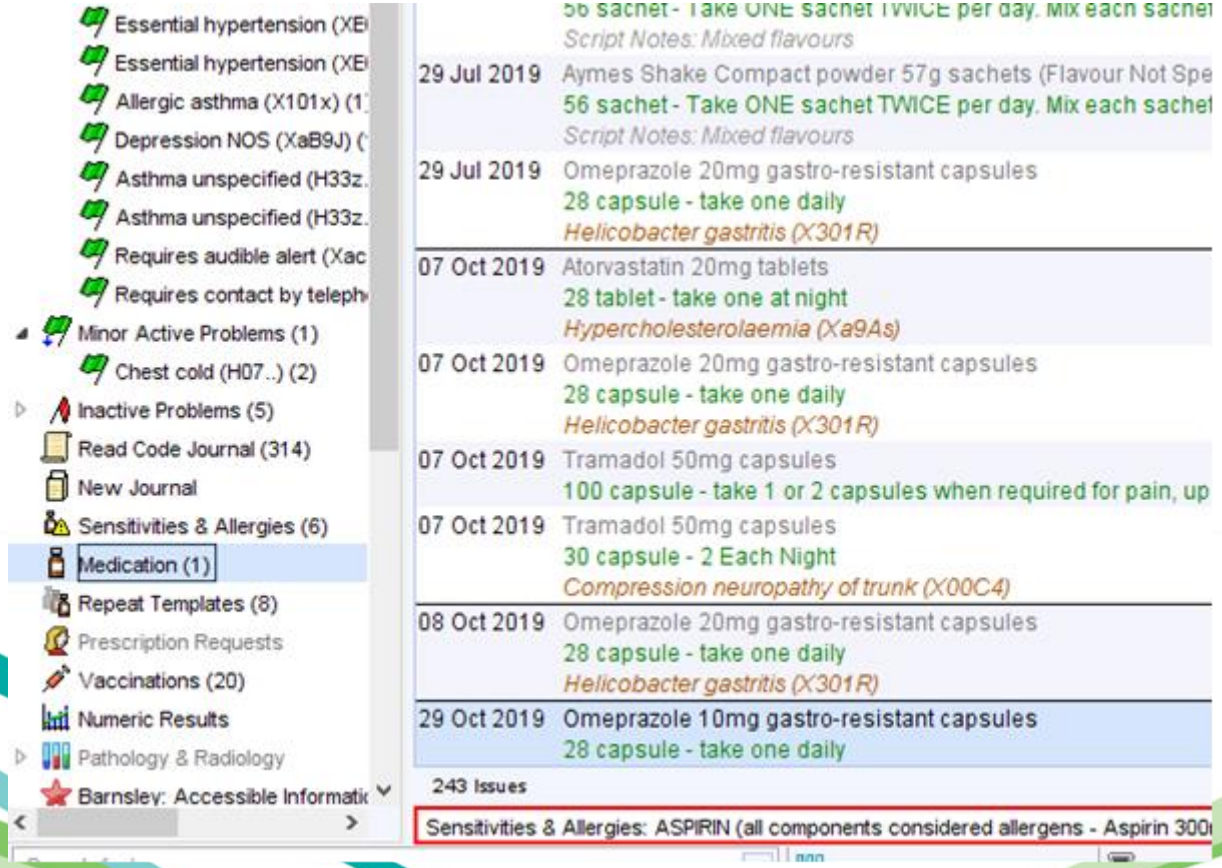
- Be aware and proactively ask about smoking status/changes in smoking behaviour:
  - Stopped or planning to stop smoking
  - Cutting down or increase in smoking
  - Using NRT, e-cigs/vaping, smokeless forms of tobacco
- Any changes SWYFT consultant psychiatrist/dispensing pharmacy should be informed.
  - Monitoring plan for side effects and toxicity
  - Plasma levels
  - Review clozapine dose

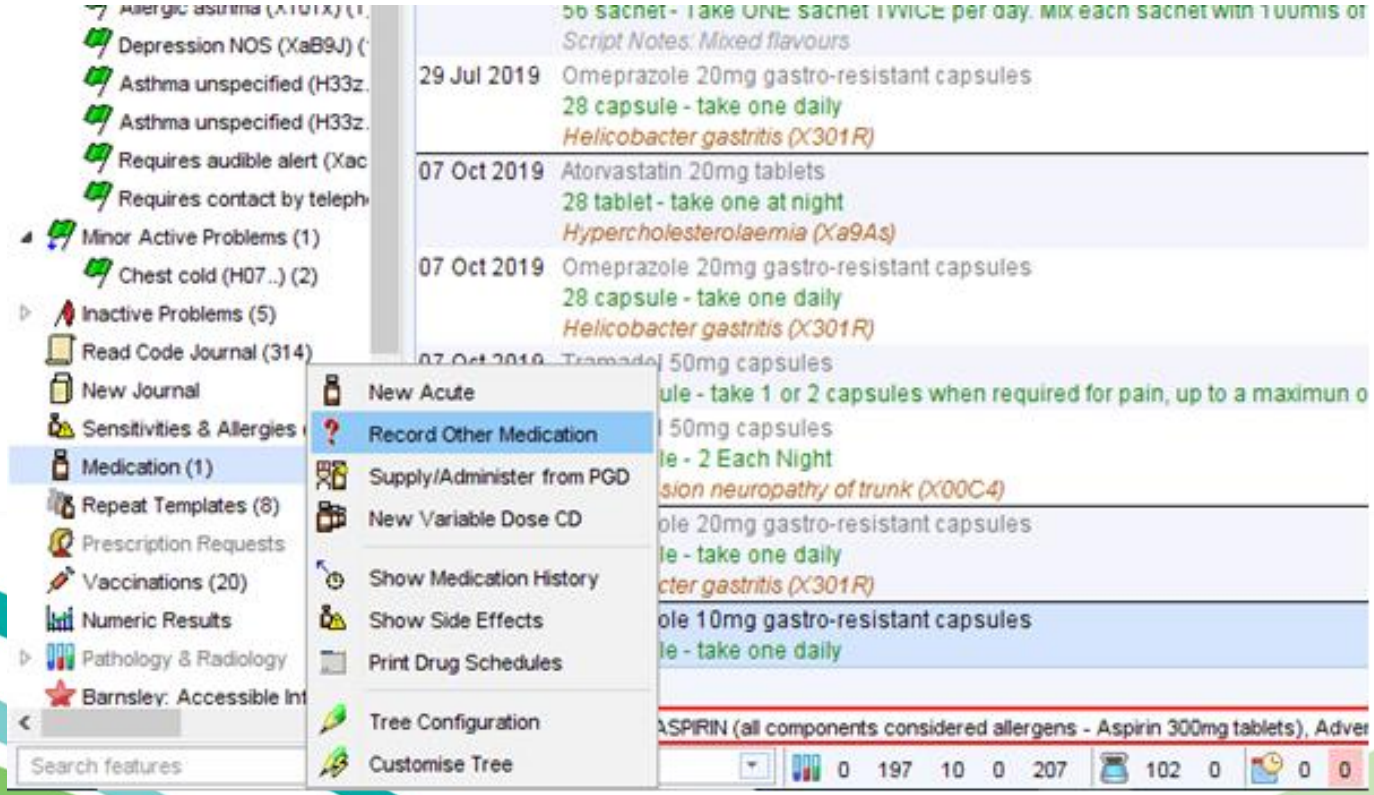


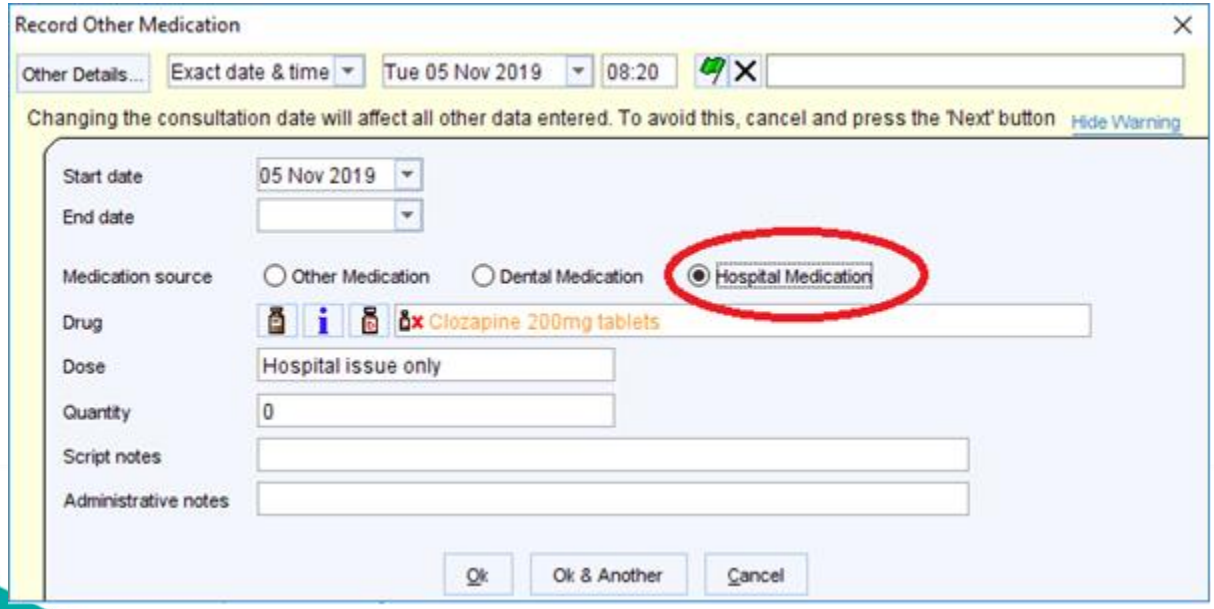
Last point!

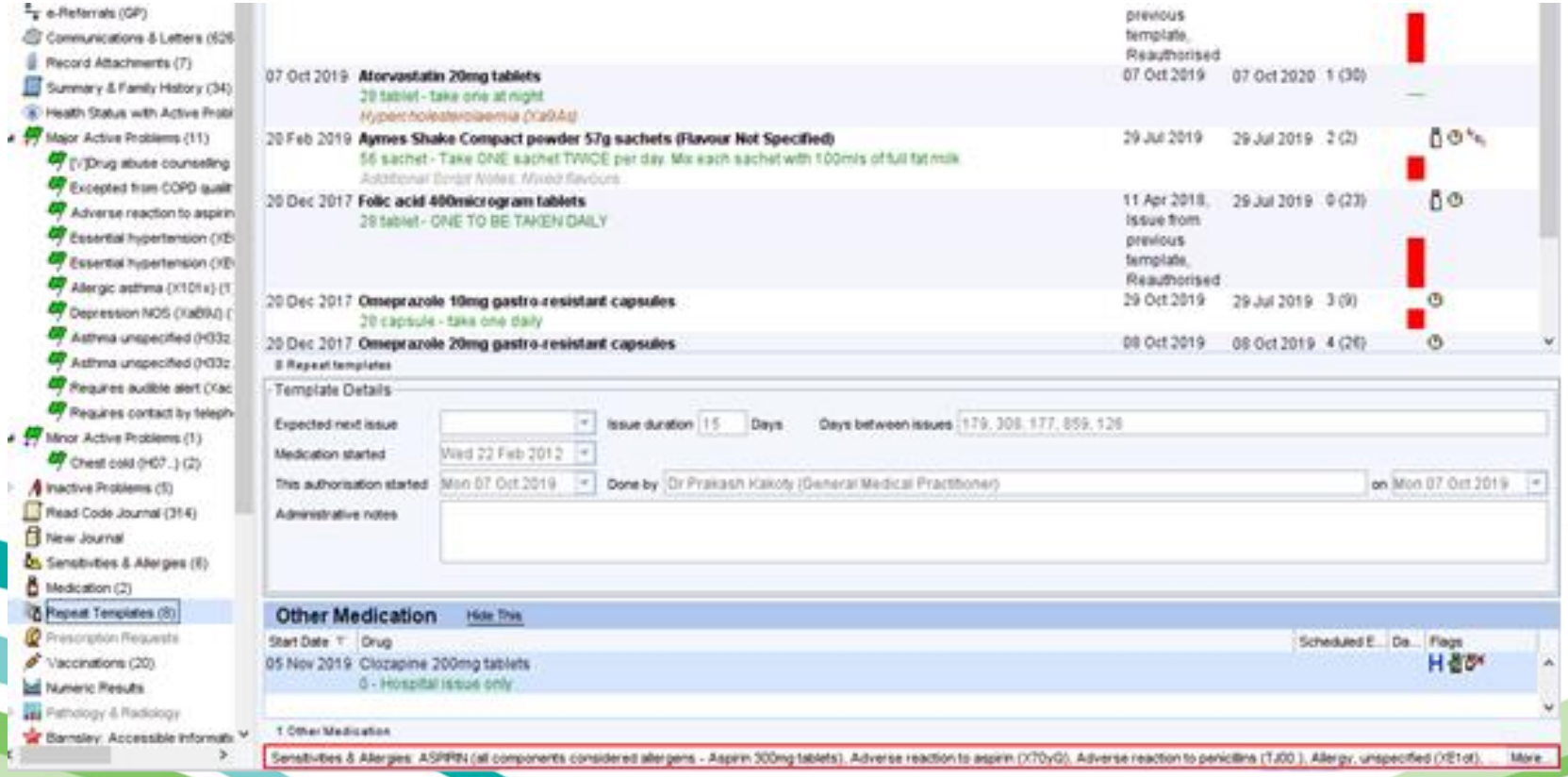
- Patients who have **missed more than 48hrs** of clozapine (accidentally or deliberately)
  - Should be advised not to restart clozapine at their previous dose
    - Loss of tolerance
  - Need urgent review by SWYFT to review treatment plan:
    - Re-titrate, starting dose 12.5mg, re-titration may need to be on a in-patient ward
    - Alternative antipsychotic
    - Monitoring mental state
    - Additional support

SystemOne
Hospital only drugs.

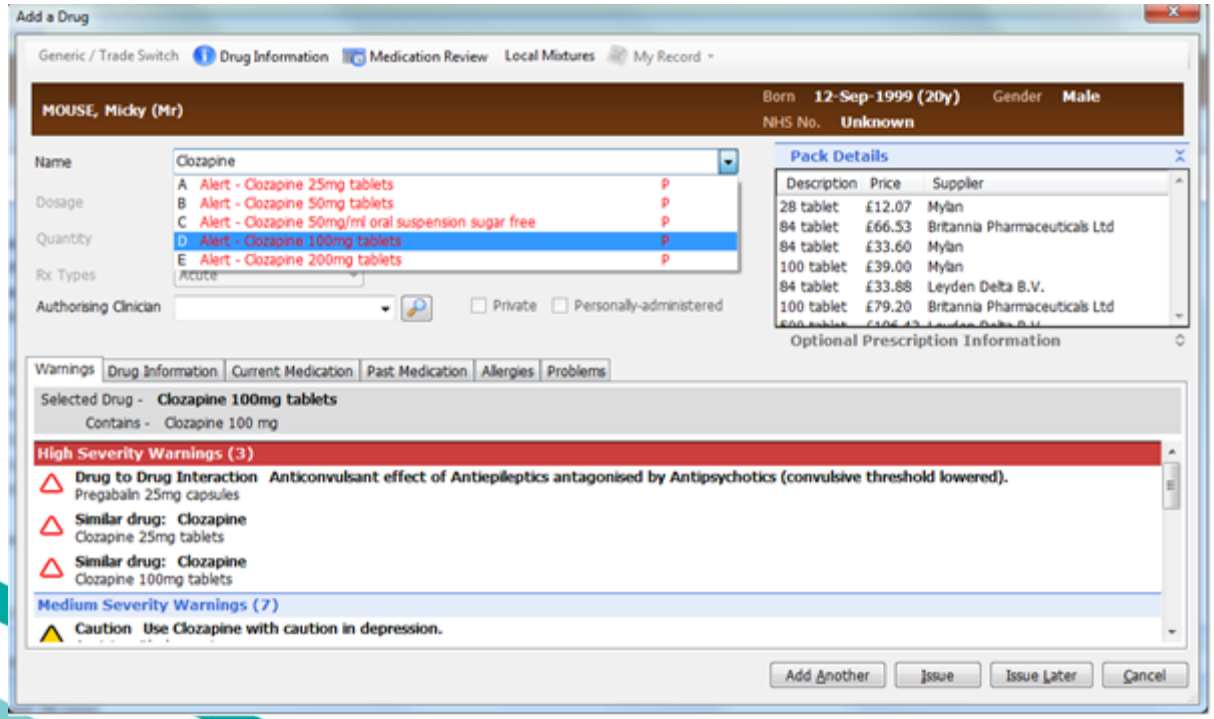


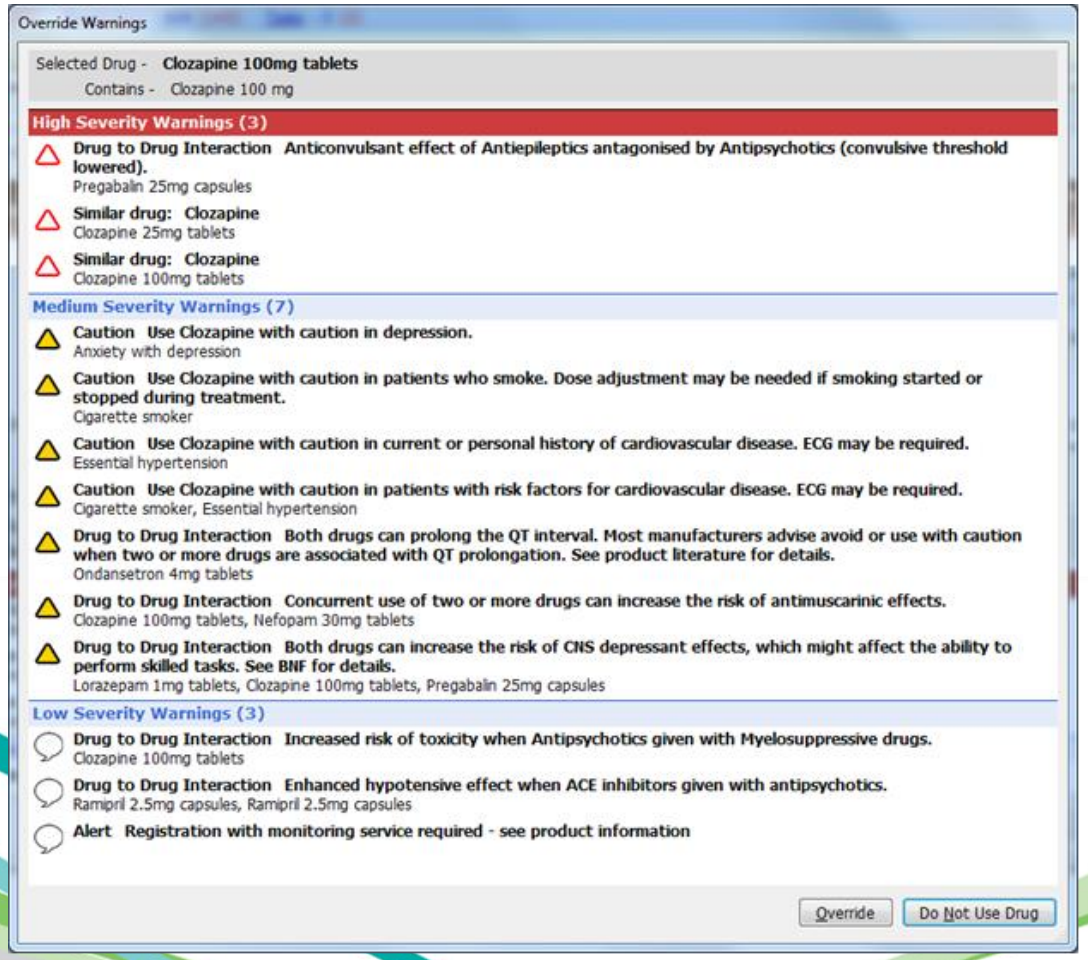

Depression NOS (XaB9J)
Asthma unspecified (H33z.
Asthma unspecified (H33z.
Requires audible alert (Xac
Requires contact by teleph
Minor Active Problems (1)
Chest cold (H07..) (2)
Inactive Problems (5)
Read Code Journal (314)
New Journal
Sensitivities & Allergies
Medication (1)
Repeat Templates (8)
Prescription Requests
Vaccinations (20)
Numeric Results
Pathology & Radiology
Barnsley: Accessible Int
Search features
New Acute
Record Other Medication
Supply/Administer from PGD
New Variable Dose CD
Show Medication History
Show Side Effects
Print Drug Schedules
Tree Configuration
Customise Tree
Script Notes: Mixed flavours
29 Jul 2019
Omeprazole 20mg gastro-resistant capsules
28 capsule - take one daily
Helicobacter gastritis (X301R)
07 Oct 2019
Atorvastatin 20mg tablets
28 tablet - take one at night
Hypercholesterolaemia (Xa9As)
07 Oct 2019
Omeprazole 20mg gastro-resistant capsules
28 capsule - take one daily
Helicobacter gastritis (X301R)
ASPIRIN (all components considered allergens - Aspirin 300mg tablets), Adver
0 197 10 0 207 102 0 0 0

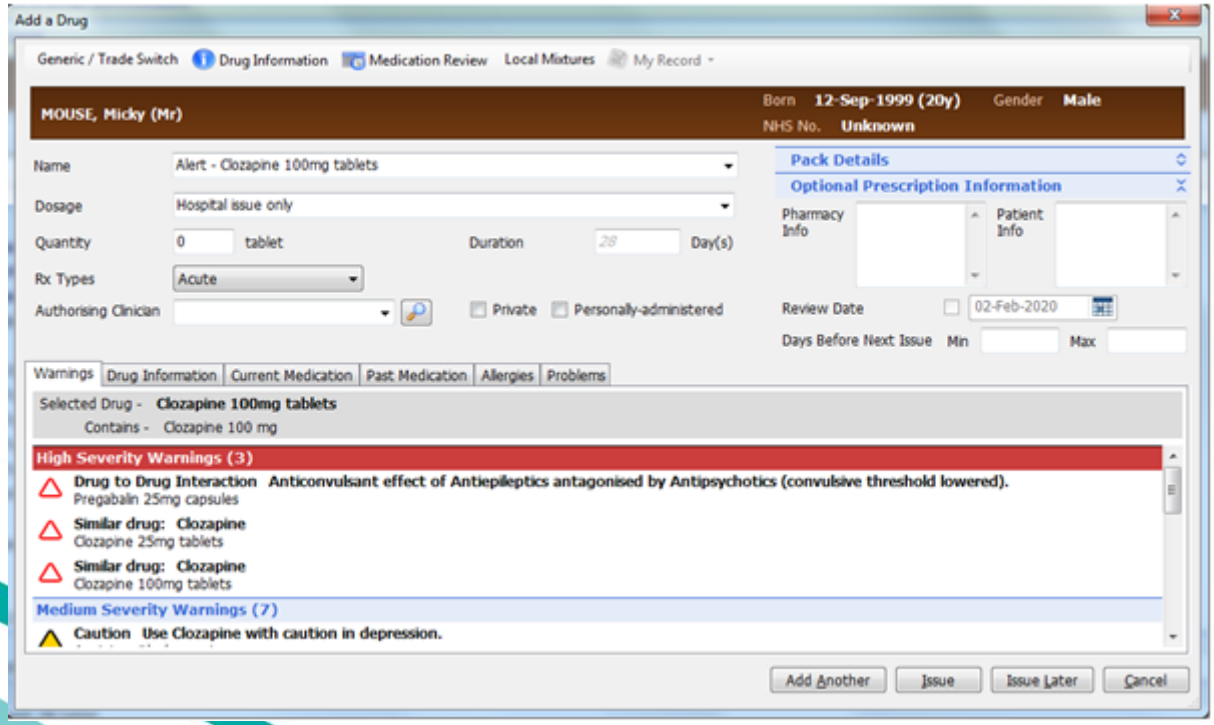

Record Other Medication
Other Details...
Exact date & time
Tue 05 Nov 2019
08:20
Changing the consultation date will affect all other data entered. To avoid this, cancel and press the 'Next' button
Hide Warning
Start date
05 Nov 2019
End date
Medication source
Other Medication
Dental Medication
Hospital Medication
Drug
Clozapine 200mg tablets
Dose
Hospital issue only
Quantity
0
Script notes
Administrative notes
Ok
Ok & Another
Cancel

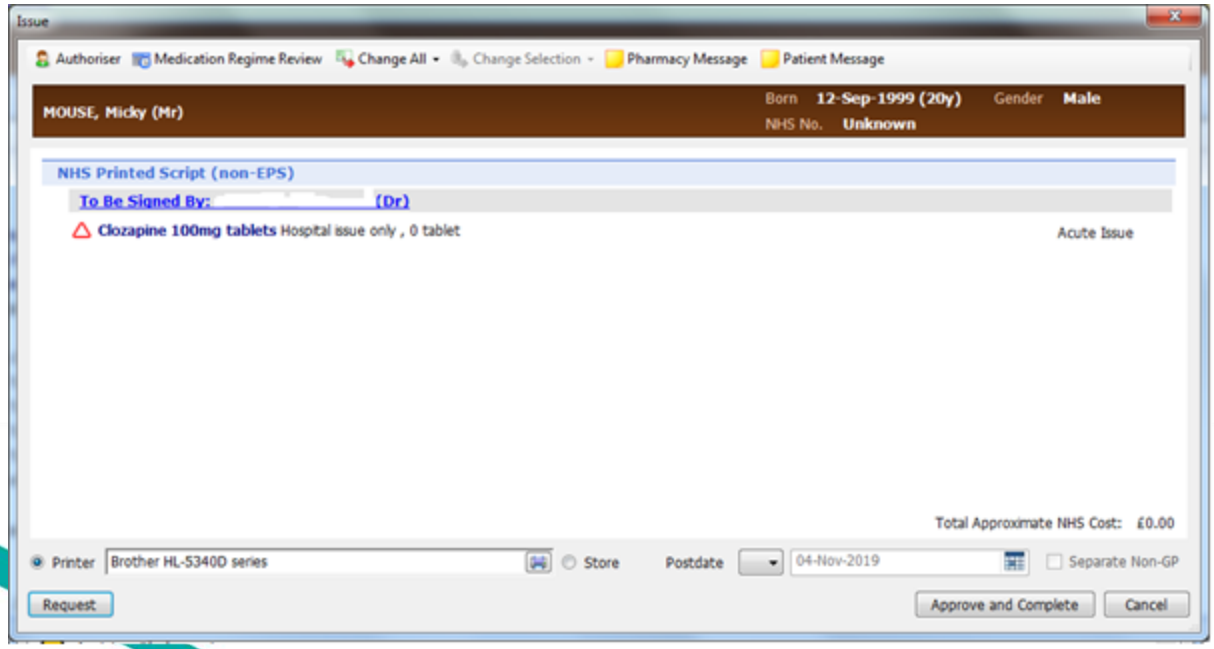

e-Referrals (GP)
Communications & Letters (626
Record Attachments (7)
Summary & Family History (34)
Health Status with Active Probl
Major Active Problems (11)
[V]Drug abuse counselling
Excepted from COPD qualit
Adverse reaction to aspirin
Essential hypertension (XE
Essential hypertension (XE
Allergic asthma (X101s) (1
Depression NOS (Xa89U) (
Asthma unspecified (H33z
Asthma unspecified (H33z
Requires audible alert (Xac
Requires contact by teleph
Minor Active Problems (1)
Chest cold (H67..) (2)
Inactive Problems (5)
Read Code Journal (314)
New Journal
Sensitivities & Allergies (8)
Medication (2)
Repeat Templates (8)
Prescription Requests
Vaccinations (20)
Numeric Results
Pathology & Radiology
Barnsley Accessible Informati
previous template, Reauthorised
07 Oct 2019 Atorvastatin 20mg tablets
28 tablet - take one at night
Hypercholesterolaemia (Xa0Ag)
07 Oct 2019 07 Oct 2020 1 (30)
20 Feb 2019 Aymes Shake Compact powder 57g sachets (Flavour Not Specified)
56 sachet - Take ONE sachet TWICE per day. Mix each sachet with 100mls of full fat milk
Additional Script Notes: Mixed flavours
29 Jul 2019 29 Jul 2019 2 (2)
20 Dec 2017 Folic acid 400microgram tablets
28 tablet - ONE TO BE TAKEN DAILY
11 Apr 2018, Issue from previous template, Reauthorised
29 Jul 2019 0 (23)
20 Dec 2017 Omeprazole 10mg gastro-resistant capsules
28 capsule - take one daily
29 Oct 2019 29 Jul 2019 3 (9)
20 Dec 2017 Omeprazole 20mg gastro-resistant capsules
08 Oct 2019 08 Oct 2019 4 (26)
8 Repeat templates
Template Details
Expected next issue
Issue duration 15 Days
Days between issues 179, 308, 177, 859, 126
Medication started Wed 22 Feb 2012
This authorisation started Mon 07 Oct 2019
Done by Dr Prakash Kakoty (General Medical Practitioner)
on Mon 07 Oct 2019
Administrative notes
Other Medication
Hide This
Start Date
Drug
Scheduled E...
Da...
Flags
05 Nov 2019 Clozapine 200mg tablets
0 - Hospital issue only
1 Other Medication
Sensitivities & Allergies: ASPIRIN (all components considered allergens - Aspirin 300mg tablets), Adverse reaction to aspirin (X70yQ), Adverse reaction to penicillins (TJ00), Allergy, unspecified (XE1df).
More...

EMIS
Hospital only drugs




Override Warnings
Selected Drug - Clozapine 100mg tablets
Contains - Clozapine 100 mg
High Severity Warnings (3)
Drug to Drug Interaction Anticonvulsant effect of Antiepileptics antagonised by Antipsychotics (convulsive threshold lowered).
Pregabalin 25mg capsules
Similar drug: Clozapine
Clozapine 25mg tablets
Similar drug: Clozapine
Clozapine 100mg tablets
Medium Severity Warnings (7)
Caution Use Clozapine with caution in depression.
Anxiety with depression
Caution Use Clozapine with caution in patients who smoke. Dose adjustment may be needed if smoking started or stopped during treatment.
Cigarette smoker
Caution Use Clozapine with caution in current or personal history of cardiovascular disease. ECG may be required.
Essential hypertension
Caution Use Clozapine with caution in patients with risk factors for cardiovascular disease. ECG may be required.
Cigarette smoker, Essential hypertension
Drug to Drug Interaction Both drugs can prolong the QT interval. Most manufacturers advise avoid or use with caution when two or more drugs are associated with QT prolongation. See product literature for details.
Ondansetron 4mg tablets
Drug to Drug Interaction Concurrent use of two or more drugs can increase the risk of antimuscarinic effects.
Clozapine 100mg tablets, Nefopam 30mg tablets
Drug to Drug Interaction Both drugs can increase the risk of CNS depressant effects, which might affect the ability to perform skilled tasks. See BNF for details.
Lorazepam 1mg tablets, Clozapine 100mg tablets, Pregabalin 25mg capsules
Low Severity Warnings (3)
Drug to Drug Interaction Increased risk of toxicity when Antipsychotics given with Myelosuppressive drugs.
Clozapine 100mg tablets
Drug to Drug Interaction Enhanced hypotensive effect when ACE inhibitors given with antipsychotics.
Ramipril 2.5mg capsules, Ramipril 2.5mg capsules
Alert Registration with monitoring service required - see product information
Override
Do Not Use Drug


Add a Drug
Generic / Trade Switch
Drug Information
Medication Review
Local Mixtures
My Record
MOUSE, Micky (Mr)
Born 12-Sep-1999 (20y)
Gender Male
NHS No. Unknown
Name
Alert - Clozapine 100mg tablets
Dosage
Hospital issue only
Quantity
0
tablet
Duration
28
Day(s)
Rx Types
Acute
Authorising Clinician
Private
Personally-administered
Pack Details
Optional Prescription Information
Pharmacy Info
Patient Info
Review Date
02-Feb-2020
Days Before Next Issue
Min
Max
Warnings
Drug Information
Current Medication
Past Medication
Allergies
Problems
Selected Drug - Clozapine 100mg tablets
Contains - Clozapine 100 mg
High Severity Warnings (3)
Drug to Drug Interaction Anticonvulsant effect of Antiepileptics antagonised by Antipsychotics (convulsive threshold lowered.
Pregabalin 25mg capsules
Similar drug: Clozapine
Clozapine 25mg tablets
Similar drug: Clozapine
Clozapine 100mg tablets
Medium Severity Warnings (7)
Caution Use Clozapine with caution in depression.
Add Another
Issue
Issue Later
Cancel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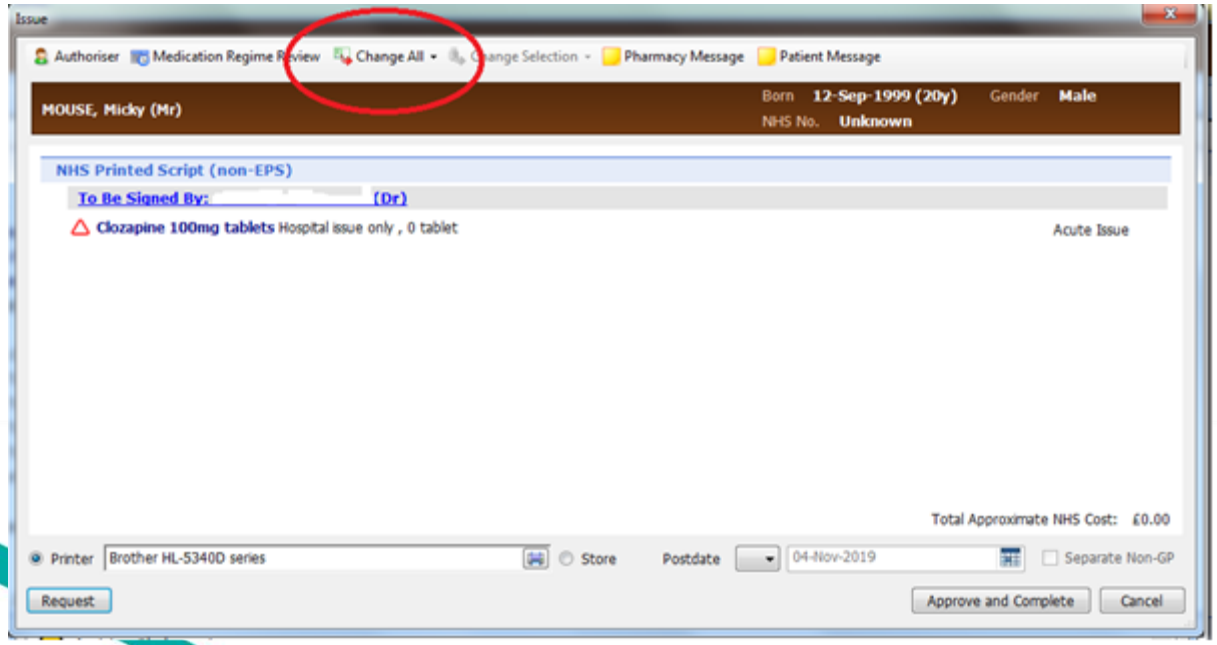
Authoriser
Medication Regime Review
Change All
Change Selection
Pharmacy Message
Patient Message
MOUSE, Micky (Mr)
Born 12-Sep-1999 (20y)
Gender Male
NHS No. Unknown
NHS Printed Script (non-EPS)
To Be Signed By: (Dr)
Clozapine 100mg tablets Hospital issue only , 0 tablet
Acute Issue
Total Approximate NHS Cost: £0.00
Printer
Brother HL-5340D series
Store
Postdate
04-Nov-2019
Separate Non-GP
Request
Approve and Complete
Cancel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Total Approximate NHS Cost: £0.00
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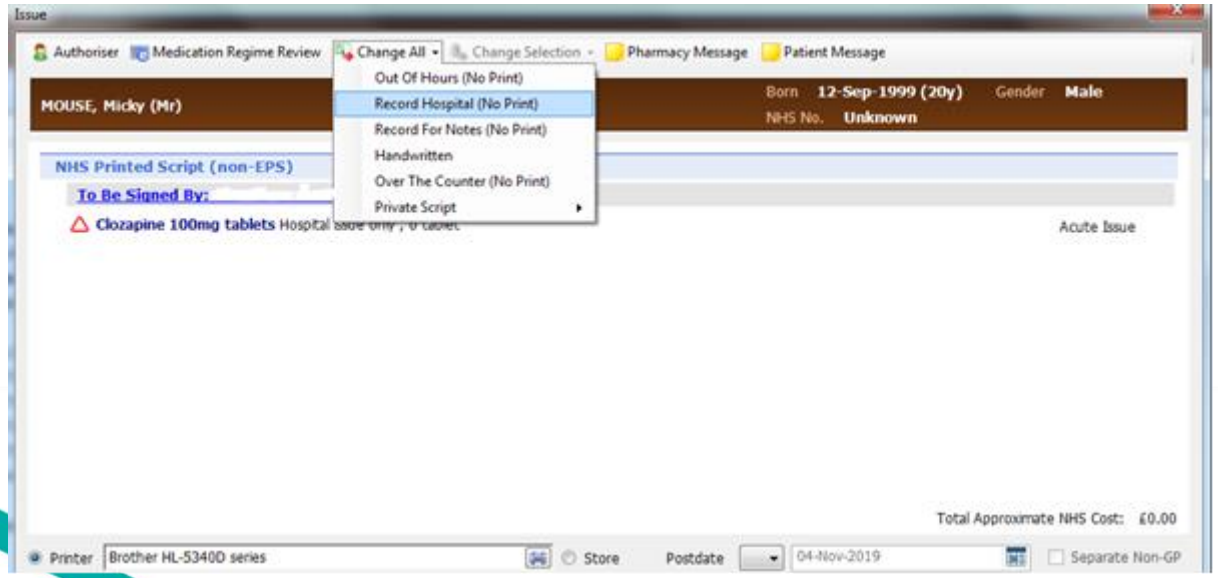
Brother HL-5340D series
Store
Postdate
04-Nov-2019
Separate Non-GP
Request
Approve and Complete
Cancel


Issue
Authoriser
Medication Regime Review
Change All
Change Selection
Pharmacy Message
Patient Message
Out Of Hours (No Print)
Record Hospital (No Print)
Record For Notes (No Print)
Handwritten
Over The Counter (No Print)
Private Script
MOUSE, Micky (Mr)
Born 12-Sep-1999 (20y)
Gender Male
NHS No. Unknown
NHS Printed Script (non-EPS)
To Be Signed By:
Clozapine 100mg tablets
Acute Issue
Total Approximate NHS Cost: £0.00
Printer
Brother HL-5340D series
Store
Postdate
04-Nov-2019
Separate Non-GP

Q	**Salbutamol 100micrograms/dose inhaler CFC free** AS REQUIRED, 2 x 200 dose
Variable use repeat	
R	**Allopurinol 300mg tablets** One To Be Taken Each Day After Food, 28 tablet
Hospital	
S	**Clozapine 100mg tablets** Hospital issue only , 0 tablet
T	CD **Lorazepam 1mg tablets** One To Be Taken At Night When Required, 28 tablet

Allergies **No allergies recorded for this patient.**

Screen Message