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Response to Coroner's Recommendation stated on letter dated 12 August 2020 ("Letter") to MIMS Australia ("MIMS").

Excerpt from the Letter (page 39)

Recommendation 2

I recommend that Pfizer Australia and Mylan Australia, in consultation with the Therapeutic Goods Administration, consider highlighting the risk of clozapine-induced gastrointestinal hypomotility in the boxed warning that appears at the beginning of their Product Information, and that if so altered, that it appears in the MIMS Full Prescribing Information and the Consumer Medicine Information.

Pursuant to the Coroner's Recommendation 2:

1. The Coroner's recommendation will be implemented in MIMS Full Prescribing Information ("MIMS FPI") and MIMS Consumer Medicine Information ("MIMS CMI") upon receipt of the revised Product Information and Consumer Medicine Information from Pfizer Australia ("Pfizer") and Mylan Australia ("Mylan").

- MIMS FPI and MIMS CMI are reproductions of the product information ("**PI**") and CMI, respectively, as supplied by pharmaceutical manufacturers and approved by the Therapeutic Goods Administration ("**TGA**"). While not altering the content, at times the MIMS FPI and MIMS CMI may differ in appearance from the approved PI and CMI provided to MIMS due to our editorial process of standardising headings and format.
- MIMS can only update MIMS FPIs and MIMS CMIs once the revised PI and CMI are available from the pharmaceutical manufacturer or TGA's Australian Register of Therapeutic Goods Public Summary ("**ARTG**"), whichever comes first.
- In view of the seriousness of the matter, MIMS will directly communicate with Pfizer and Mylan regarding the availability of the revised PIs and CMIs of Clopine and Clozaril, respectively.
- MIMS endeavours to ensure that published MIMS FPI and MIMS CMI are accurate and current. The target turn-around time for MIMS FPI and MIMS CMI updates is two (2) months or less from the receipt of updates from the pharmaceutical manufacturer or from its publication on the ARTG, whichever comes first. In this case, MIMS will prioritise these updates and endeavour to publish them electronically on the 1st day of the month following receipt of the updated PIs and CMIs.

2. In addition to the Coroner's recommendation, MIMS Abbreviated Product Information ("MIMS API") will be updated.

- Being the proprietor of MIMS API, MIMS has reviewed and revised the Precautions section of the Clopine and Clozaril MIMS APIs.
- The MIMS API is an abbreviated medicines information monograph sourced from the PI as well as other references such as the World Anti-Doping Agency and the TGA Pregnancy database.

- MIMS has updated the MIMS API of Clozapine and Clozaril in the MIMS' publications indicated below to include **monitoring for serious GI effects such as hypomotility** in the "Precautions" section:
  (i) MIMS Abbreviated Feb/Mar 2021 book to be published on 1st March 2021; and
  (ii) MIMS electronic products (ie MIMS Online, MIMS Mobile Apps, eMIMS Classic, and eMIMS Cloud) with effect from 1st January 2021.
- Please refer to Appendix A attached for the revised MIMS API of Clopine and Clozaril reflecting these changes.

Ⓜ CLOPINE clozapine ⚡ (C★) Pfizer
(Comarketed with Douglas; Authorised medical practitioner only)

Myocarditis/cardiomyopathy. Cases of myocarditis, some of which have been fatal, and cardiomyopathy have been reported in patients on clozapine (see Section 4.4 Special Warnings and Precautions for Use; Section 4.8 Adverse Effects (Undesirable Effects)). If myocarditis or cardiomyopathy is suspected, clozapine treatment should be stopped and the patient immediately referred to a cardiologist. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with clozapine.

Use: Atypical antipsychotic (tricyclic dibenzodiazepine derivative). Treatment resistant schizophrenia in patients nonresponsive to, intolerant of other antipsychotics
Contra: Drug induced granulocytopenia, agranulocytosis history; bone marrow disorder; circulatory collapse; CNS depression; alcoholic, toxic psychosis; drug intoxication; coma; uncontrolled epilepsy; severe renal, cardiac (eg myocarditis), hepatic disease (incl active hepatic disease assoc with nausea, anorexia, jaundice; progressive hepatic disease; hepatic failure); paralytic ileus; inability to undergo regular blood tests
Prec: Pretreatment WCC ≤ 3500/mm^3, abnormal differential blood count/ ANC (do not initiate); monitor WCC, ANC (mandatory; ≤ 10 days pretreatment, wkly for 1st 18 wks, then at least mthly + 1 mth post-therapy; see full PI for incr monitoring if therapy interrupted, blood dyscrasia occurs), lipids, LFTs, bowel habit, for serious GI effects (eg GI hypomotility), hyperglycaemia, weight, infection, fever, myocarditis, suicidality, akathisia; eosinophils > 3000/mm^3 (disc, restart when < 1000/mm^3); platelets < 50,000/mm^3 (disc); WCC < 3000/mm^3 and/or ANC < 1500/mm^3 (disc); previous clozapine disc due to WBC deficiency (must not re-expose); clozapine assoc myocarditis/ cardiomyopathy (should not rechallenge, see full PI); bone marrow disorder history; seizure history, predisposition; sleep apnoea history, risk; prolonged QT, heart failure family history (pretreatment cardiac evaluation); stroke risk; CV, renal, hepatic disorder; rapid dose escalation; dose > 450 mg/day; VTE risk factors (identify incl pretreatment); abrupt withdrawal; prostatic enlargement, narrow angle glaucoma; prediabetes, diabetes incl risk eg obesity, family history (monitor fasting BGL); immobilisation (avoid); incr fall risk (assess pretreatment, recurrently); smoking cessation; elderly ≥ 60 yrs (esp with dementia related psychosis, CV/ pulmonary condition); women of childbearing potential (ensure adequate contraception); pregnancy esp 3rd trimester; lactation (should not breastfeed); children < 16 yrs
Adverse: Fatigue; dizziness; hypersalivation; tachycardia; GI upset esp constipation; dry mouth; blood dyscrasia; fever; infection; incr LFTs; seizure; sedation; MI; hyperthermia; orthostatic hypotension, falls; hypertension; syncope; headache; psychotic disorder; dysarthria; blurred vision; rigidity, tremor, akathisia; NMS (disc); urinary incontinence, retention; weight gain, hyperglycaemia, dyslipidaemia; megacolon, intestinal infarction/ ischaemia, ulceration, perforation; DRESS; rare: myocarditis, pericarditis, arrhythmia, respiratory depression, pneumonia, pancreatitis, hepatitis, obesity, sleep apnoea syndrome, cholestatic jaundice, thromboembolism; very rare: cardiomyopathy, cardiac arrest; others, see full PI
Interact: Other antipsychotics esp long acting depots (avoid); benzodiazepines incl recent use; anticonvulsants incl carbamazepine (avoid), valproic acid; CNS depressants incl alcohol, narcotics, antihistamines; antidepressants incl SSRIs, venlafaxine, MAOIs; OCs; bone marrow, respiratory depressants; anticholinergics; hypotensives; highly protein bound drugs eg warfarin, digoxin; CYP1A2, 2D6, 3A4 inhibitors/ inducers (eg macrolides, ciprofloxacin, cimetidine, azole antimycotics, protease inhibitors, phenytoin, rifampicin, St John's wort, caffeine, PPIs, tobacco smoke); CNS active agents incl lithium; adrenaline and derivatives; norfloxacin, enoxacin; drugs causing electrolyte imbalance, prolonged QT, incr fall/ seizure risk; CYP2D6 substrates eg phenothiazines, type IC antiarrhythmics (poss)
TABLETS (S4) Clozapine; lactose monohydrate; yellow, scored Δ⊗
Dose ±Ⓜ Individualise dose; disc other antipsychotic over ≈ 1 wk, wait ≥ 24 hrs before initiation (pref). Use lowest effective dose
Initially 12.5 mg 1-2 times daily on day 1; 25 mg 1-2 times daily on day 2; if well tolerated incr slowly in 25-50 mg increments up to 300 mg/day within 2-3 wks; thereafter may incr by 50-100 mg/wk (pref) or half wk; therapeutic dose range 200-450 mg/day in divided doses, max 600-900 mg/day. May admin larger portion of divided dose at bedtime
Elderly, seizure history, CV/ renal/ hepatic disorder: initially 12.5 mg once on day 1; incr dose slowly in small increments; max dose increment in elderly 25 mg/day
Maintenance. After achieving max therapeutic benefit, may carefully titrate downward to 150-300 mg/day in divided doses. May admin ≤ 200 mg/day as single evening dose
Disc: taper over 1-2 wks. Interruption > 2 days since last dose: complex, see full PI
Pack: 25 mg [100]
Pack: 50 mg [100]
Pack: 100 mg [100]
Pack: 200 mg [100]
Pack: 25 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Community Access (MP)
PBS: $76.38
Pack: 50 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Community Access (MP)
PBS: $142.20
Pack: 100 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Community Access (MP)
PBS: $259.82
Pack: 200 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Community Access (MP)
PBS: $511.90
Pack: 25 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Private (MP)
PBS: $76.38
Pack: 50 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Private (MP)
PBS: $142.20
Pack: 100 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Private (MP)
PBS: $259.82
Pack: 200 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Private (MP)
PBS: $511.90
Pack: 25 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Public (MP)
PBS: $64.64
Pack: 50 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Public (MP)
PBS: $129.28
Pack: 100 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Public (MP)
PBS: $242.38
Pack: 200 mg [100] x 2: Section 100 (Highly Specialised Drugs) - Public (MP)
PBS: $484.76
CLOPINE ORAL SUSPENSION (S4) Deleted, March 2020

Ⓜ CLOZARIL clozapine ⚡ (C★) Mylan Health
(Authorised medical practitioner only)

Warning. Cases of myocarditis, some of which have been fatal, and cardiomyopathy have been reported in patients on clozapine (see Section 4.4 Special Warnings and Precautions for Use; Section 4.8 Adverse Effects (Undesirable Effects)). If myocarditis or cardiomyopathy is suspected, Clozaril treatment should be stopped and the patient immediately referred to a cardiologist. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with Clozaril.

Use: Atypical antipsychotic (tricyclic dibenzodiazepine derivative). Treatment resistant schizophrenia (patients nonresponsive to, or intolerant of, ≥ 2 other antipsychotics)
Contra: Drug induced granulocytopenia/ agranulocytosis history; bone marrow disorder; circulatory collapse; CNS depression; alcoholic, toxic psychoses; drug intoxication; coma; uncontrolled epilepsy; severe renal, cardiac (eg myocarditis), hepatic (incl active hepatic disease assoc with nausea, anorexia, jaundice; progressive hepatic disease; hepatic failure) disease; paralytic ileus; inability to undergo regular blood tests
Prec: Pretreatment WCC ≤ 3.5 x 10^9/L, abnormal differentials, ANC (do not initiate); monitor WCC, ANC (mandatory; within 10 days pretreatment, wkly for 1st 18 wks, then at least mthly + 1 mth post-therapy, see full PI), lipids, LFTs, weight, for serious GI effects (eg GI hypomotility), constipation (manage effectively at onset), hyperglycaemia, infection (eg flu-like symptoms), fever (evaluate cause), akathisia; treatment interruption after > 18 wks therapy (monitor WCC, ANC wkly for additional 6 wks (if > 3 days interruption) or 18 wks (if > 4 wks interruption); eosinophils > 3 x 10^9/L (disc, restart when < 1 x 10^9/L), platelets < 50 x 10^9/L, WCC < 3 x 10^9/L, ANC < 1.5 x 10^9/L during therapy (disc; see full PI for additional monitoring); previous clozapine disc due to WBC deficiency (must not re-expose); treatment initiation, high suicidality risk (close supervision); heart failure family history (pretreatment cardiac evaluation), QT prolongation; history of clozapine assoc myocarditis/ cardiomyopathy (should not rechallenge, see full PI); bone marrow disorder history (pretreatment haematology review); renal, hepatic, CV impairment; prostatic enlargement; narrow angle glaucoma; prediabetes, diabetes incl risk eg family history, obesity (monitor fasting BGL); stroke risk; epilepsy; seizure history, predisposition; sleep apnoea history, risk; dementia; rapid dose escalation; abrupt withdrawal; smoking cessation; dose > 450 mg/day; prolonged therapy; VTE risk factors (identify incl pretreatment); condition that incr fall risk (assess pretreatment, recurrently); elderly ≥ 60 yrs (esp with dementia related psychosis, CV/ pulmonary conditions); women of childbearing potential (ensure adequate contraception); pregnancy esp 3rd trimester; lactation (should not breastfeed); children < 16 yrs
Adverse: Fatigue; dizziness; hypersalivation; tachycardia; GI upset esp constipation; dry mouth; blood dyscrasia; fever; infection; incr LFTs; seizure; sedation; MI; hyperthermia; orthostatic hypotension, falls; hypertension; syncope; headache; psychotic disorder; dysarthria; blurred vision; rigidity, tremor, akathisia; NMS (disc); urinary incontinence, retention; weight gain, hyperglycaemia, dyslipidaemia; megacolon, intestinal infarction/ ischaemia, ulceration, perforation; DRESS; rare: myocarditis, pericarditis, arrhythmia, respiratory depression, pneumonia, pancreatitis, hepatitis, obesity, sleep apnoea syndrome, cholestatic jaundice, thromboembolism; very rare: cardiomyopathy, cardiac arrest; others, see full PI
Interact: Other antipsychotics esp long acting depots (avoid); benzodiazepines (incl recent use); carbamazepine (avoid); AEDs eg valproic acid; CNS active agents eg lithium; CNS (eg narcotics, antihistamines, alcohol), bone marrow, respiratory depressants; hypotensives; anticholinergics; adrenaline incl derivatives; CYP450 (eg cimetidine, ciprofloxacin, clarithromycin, erythromycin), 1A2 (eg caffeine), 3A (eg protease inhibitors, azole antimycotics) inhibitors; azithromycin; enoxacin; norfloxacin; CYP1A2 (eg tobacco smoke), 3A4 inducers (eg phenytoin, rifampicin, St John's wort); highly protein bound drugs eg digoxin, warfarin; PPIs; SSRIs; MAOIs; venlafaxine; OCs; drugs causing prolonged QT, electrolyte imbalance; CYP2D6 substrates eg antidepressants, phenothiazines, type IC antiarrhythmics (theoretical)
TABLETS (S4) Clozapine; lactose monohydrate, maize starch; yellow scored Δ
Dose Individualise dose; use lowest effective dose
Initially 12.5 mg 1-2 times daily on day 1; 25 mg 1-2 times daily on day 2; if well tolerated may incr slowly in 25-50 mg increments up to 300 mg/day within 2-3 wks; thereafter may incr by 50-100 mg/wk (pref) or half wk; therapeutic dose range 200-450 mg/day in divided doses (admin larger portion at bedtime if doses uneven), max 600-900 mg/day
Maintenance. After achieving max therapeutic benefit, maintain on lower dose if poss: carefully titrate down to 150-300 mg/day in divided doses; may admin dose ≤ 200 mg/day as single evening dose
Elderly. Day 1: 12.5 mg once daily; may incr by max 25 mg/day
CV, renal, hepatic disorder; seizure history. Day 1: 12.5 mg once daily; may incr slowly in small increments
Disc. Gradually withdraw over 1-2 wks
Treatment interruption: reinitiate if > 2 days since last dose; see full PI
Switching from other antipsychotic: see full PI

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