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Ref: H201603159

Dear

# Response to your request for official information

Thank you for your request of 3 August 2016 under the Official Information Act 1982 (the Act) for "a copy of this report please – 4.1.6 Special Reports: Annual Review of Fatalities (January 2015 – December 2015)" with reference to item 4.1.6 of the 166<sup>th</sup> Medicines Adverse Reactions Committee (MARC) meeting minutes. The report requested is included in the quarterly report provided by the Centre for Adverse Reactions Monitoring (CARM).

The information relating to this request is itemised below, with a copy of the document attached.

I have decided under sections 9(2)(a) and 9(2)(ba)(i) of the Act to withhold information in order to protect the privacy of natural persons and to protect information which is subject to an obligation of confidence where the making available of the information would be likely to prejudice the supply of similar information.

Request	Response
A copy of the following report presented	Attached is:
to the MARC (item 4.1.6 of the 166 <sup>th</sup>	1. A copy of the report presented to
MARC meeting - Special Reports:	the MARC (item 4.1.6 of the 166 <sup>th</sup>
Annual Review of Fatalities)	MARC meeting).

Please note that the date column of the quarterly report reflects the date that the adverse reaction was reported to CARM, not the date that the adverse reaction occurred. Age is listed in years unless specified in months which is identified with 'm', for example 6m indicates the patient is six months old.

I trust this information fulfils your request. You have the right, under section 28 of the Act, to ask the Ombudsman to review my decision to withhold information under this request.

Yours sincerely



Section 5: Special Reports

### Annual Review of Fatalities (January 2015 – December 2015)

#### Overview

There were 136 reports of death submitted to CARM in the context of medicine use involving 166 medication administrations (i.e. more than one medication may be implicated in each report). In 70% of cases (n=95) a causal relationship to the medicine(s) identified was assessed as either unrelated (47%) or the cause of death was unclassifiable (23%). In 30% of reports (n=41), the medicine was assessed as potentially contributing to the death (n=28) or resulted in an enverse reaction(s) that likely caused the death (n=13) (Table 1). Overview of the deaths that are likely due to the medication is discussed under Table 6 below. These proportions are similar to those reported fast year.

The most frequent ATC group of medicines represented by the 166 medicines in the 136 reports was "Nervous System" (n=76). "Blood and Blood forming organs" (n=27), "Antineoplastics and Immunomodulating Agents" (n=26) and "Anti-infectives" (n=17) were the other groups of note. The remaining ATC groups involved 20 medicines collectively with only a few medicines in each class, (Tables 2 & 3). In the Nervous System ATC group 60 of the 76 reports are for clozapine which are from Pharma consequent on a review of their database. Only 3 of the reports could be assigned to the 'may be contributory' causal association with the remainder either documenting events that were unrelated or with too little information to determine an association.

Table 4 illustrates the age distribution of all fatal reports to CARM irrespective of causality. Fifty-six percent of the reports where the age was known, were in patients older than 65 years and 11% were older than 80 years. There were more males (55%) compared to females (45%). There were 5 reports in patients under the age of two. These reports were for 3 cases of sudden death/Sudden Unexpected Death in Infancy in the context of routine childhood immunization schedule with 2 occurring 18 days following the 6 week routine scheduled vaccines, one of which also had developed septicemia and the third 21/2 weeks after the 6 month routine scheduled vaccines. The remaining two reports; one was attributed to misoprostol associated Moebius Syndrome following a failed termination in the first trimester and the second, a Pharma report, detailed an unspecified brain injury in a 2 year old who received eculizumab for an off-label indication. The causal association could not be determined. There were 2 deaths in the 2-10 year age group. One report documented a suicide with levetiracetam occurring on changing brands. The potential for severe psychiatric reactions with levetiracetam is well recognized and the brand related association was investigated but was not considered to be a factor. In the other report a 14 year old developed fatal bronchiectasis whilst being treated with tocilizumab. The patient had a long history of bronchiectasis since infancy and although the report had limited information, the underlying condition was thought to be the primary cause of death.

Table 5 lists the 136 reports of fatalities to CARM grouped by ATC group. In 70% of these reports the cause of death was assessed as unrelated or unclassifiable and in the remaining 30% the medicine may have contributed to or was likely to have caused the reaction that led to death. For many of the reports of death the cases relate either to reactions that are well recognized and/or involve complex co-morbidity that may have increased the risk of death. Of the reactions reported most frequently bleeding episodes accounted for 7/13 (54%) of reports where death was assessed as due to the medication and 8/28 (29%) of reports where the medicine may have been contributory. The remainder was of diverse drug/reaction combinations.

Table 6 is a subset of the data in Table 5

## Table 1: Outcome Overview

Outcome	Number of Cases	Percentage
Died due to the adverse reaction	13	9.6
Died – drug may be contributory	28	20.6
Died – unrelated to the drug	64	47.0
Died – cause unclassifiable	31	22.8
Total Reports	136	100.0

## Table 2: ATC classification Overview

Table 2: ATC classification Overview	65	JUL A
ATC High Level Group	No. of Mediciness	Rercentage
Alimentary	3 16	1.8
Blood and Blood forming organs	27 111	16.3
Cardiovascular	17115	4.2
Dermatological	1 Dall	
Genito Urinary System and Sex Hormones	KINTER	0.6
Systemic Hormones (excl Sex Hormones)	2	1.2
Anti-infectives	17	10.2
Antineoplastics and Immunomodulating Agents	26	15.7
Musculoskeletal	7	4.2
Nervous System	76	45.8
Antiparasitic Products, Insecticides and Repellents	0	
Respiratory System	0	
Sensory Organs	0	
Miscellaneous	0	
Total Suspect Medicines	166	100.0

	ATC Group	No. of Medicines	Total
Α	Alimentary		3
A02	Misoprostol	1	
	Omeprazole	1	
A04	Ondansetron hydrochloride	1	
В	Blood and Blood forming organs		27
B01	Apixaban	2	
	Dabigatran	15	
	Heparin LMW – Enoxaparin	2	
	Rivaroxaban	3	2
	Ticagrelor	2	2
	Warfarin	2	5
B02	Eptacog alpha		(
C	Cardiovascular	- AD	R
C01	Amiodarone	KOL V C	
C03	Frusemide	AN' N	15
C09	Cilazapril	AV ZALA	
009	Quinapril		
C10	Atorvastatin		
CIU		EIL	
0	Rosuvastatin	ID/VI	all and a second second
G	Genito Urinary System and Sex Hormones		1
G03	Cyproterone acetates	1	
H	Systemic Hormones (exc) Sex Hormones)		2
H02	Prednisone	1	
H05	Teriparatide	1	
J	Anti-infectives		17
J01	Alucioxadillin	1	
1	Gentamycin	1	
AL	Nitrofurantoin	1	
241-	Trimethoprim	1	
105	Gancidovir sodium	1	
J07	DTaP-Hexa Vaccine	3	1
	Hafluenza – Trivalent	3	
212	Pheumococcal 13	3	
20	Rota Virus Vaccine	3	
Y	Antineoplastics and Immunomodulating Agents		26
L01	Azacitidine	1	
	Bevacizumab	1	
	Erlotinib	1	
	lbrutinib	1	
	Methotrexate	1	
	Pembrolizumab	3	
/	Rituximab	1	
L02	Abiraterone	1	
	Tamoxifen	1	
L04	Adalimumab	2	
<b>LV</b> <sup>-</sup> <b>I</b>	Eculizumab	1	
	Infliximab	1	
	Lenalidomide	6	
	Thalidomide	3	
		3	

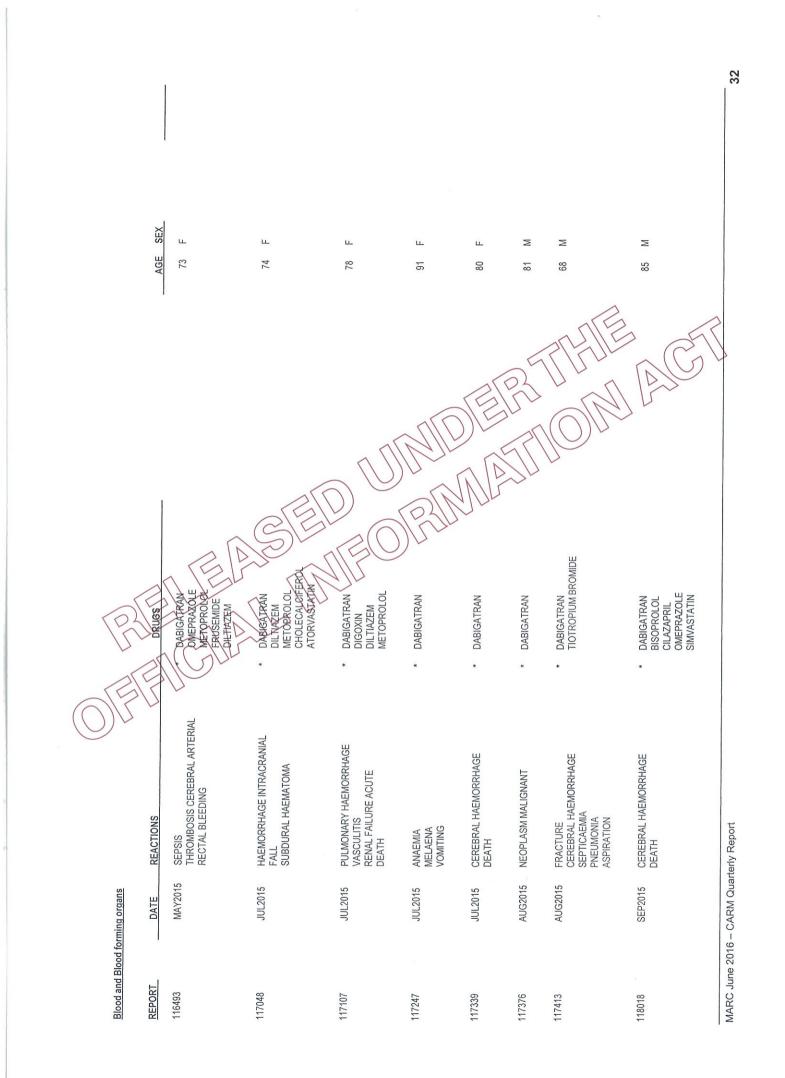
# Table 3: ATC Detailed listing of Medicines

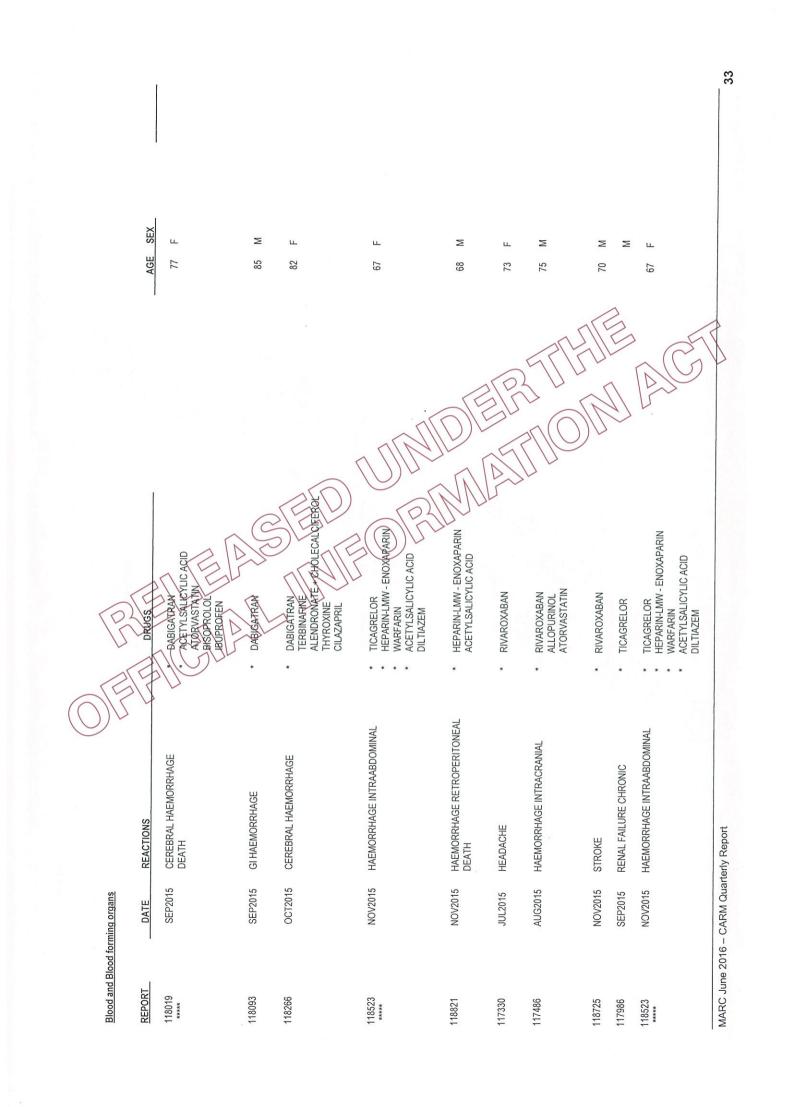
MMusculoskeletalM01DiclofenacIbuprofenM03RocuroniumM05ZoledronateNNervous SystemN01FentanylN02Acetylsalicyclic acidN03ClonazepamLamotrigineLevetiracetamN04Benztropine Mesylate	7       3       1       1       2       76       1       2       1       1       1       1       1       1       1       1       1       1       1       1       1       1
M01DiclofenacIbuprofenM03RocuroniumM05ZoledronateNNervous SystemN01FentanylN02Acetylsalicyclic acidN03ClonazepamLamotrigineLevetiracetam	3 1 1 2 76 1 2 76 1 1
M03       Rocuronium         M05       Zoledronate         N       Nervous System         N01       Fentanyl         N02       Acetylsalicyclic acid         N03       Clonazepam         Lamotrigine       Levetiracetam	1 1 2 76 1 2 1
M05ZoledronateNNervous SystemN01FentanylN02Acetylsalicyclic acidN03ClonazepamLamotrigineLevetiracetam	2 76 1 2 1 1
NNervous SystemN01FentanylN02Acetylsalicyclic acidN03ClonazepamLamotrigineLevetiracetam	1         76           2         1           1         1
N01     Fentanyl       N02     Acetylsalicyclic acid       N03     Clonazepam       Lamotrigine     Levetiracetam	1         76           2         1           1         1
N02     Acetylsalicyclic acid       N03     Clonazepam       Lamotrigine       Levetiracetam	<u>2</u> 1
N03 Clonazepam Lamotrigine Levetiracetam	1
N03 Clonazepam Lamotrigine Levetiracetam	1
Levetiracetam	1
Levetiracetam	
N04 Benztropine Mesylate	1
	1 15
N05 Clozapine	6,0
Haloperidol	
Olanzapine	
Quetiapine	
Risperidone	
N06 Fluoxetine	
Paroxetine	
Sertraline	NIL EUR
Total Medicines	166

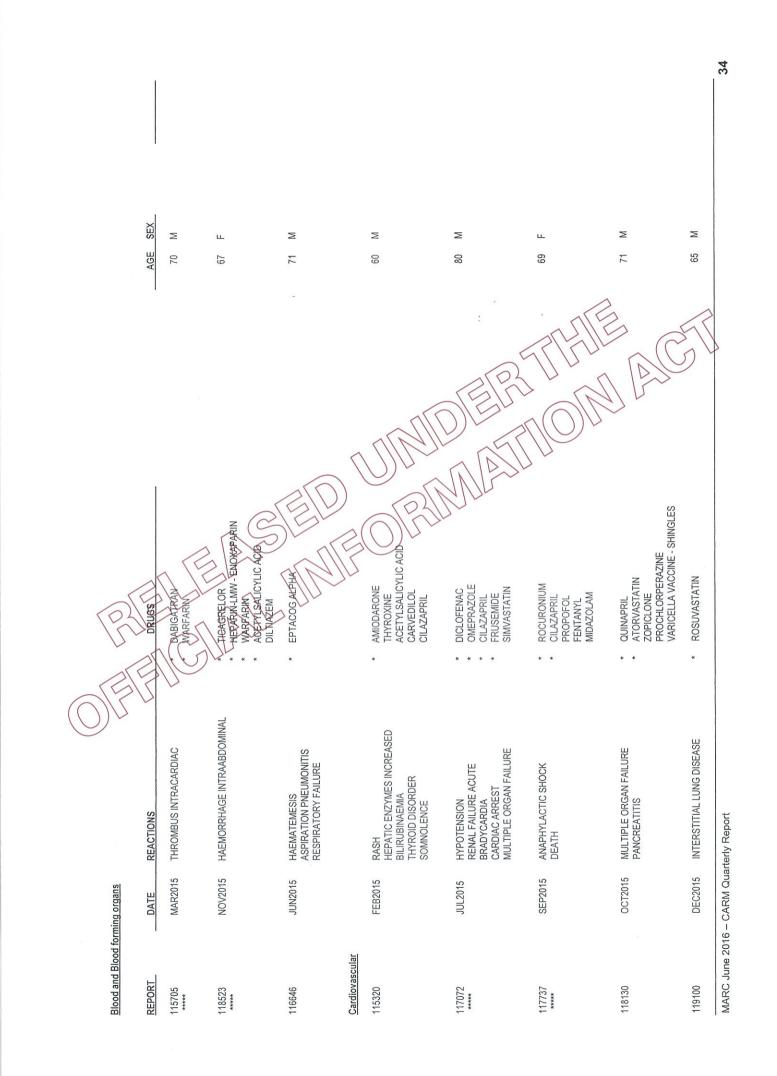
Table 4: Age group and Gender Overview

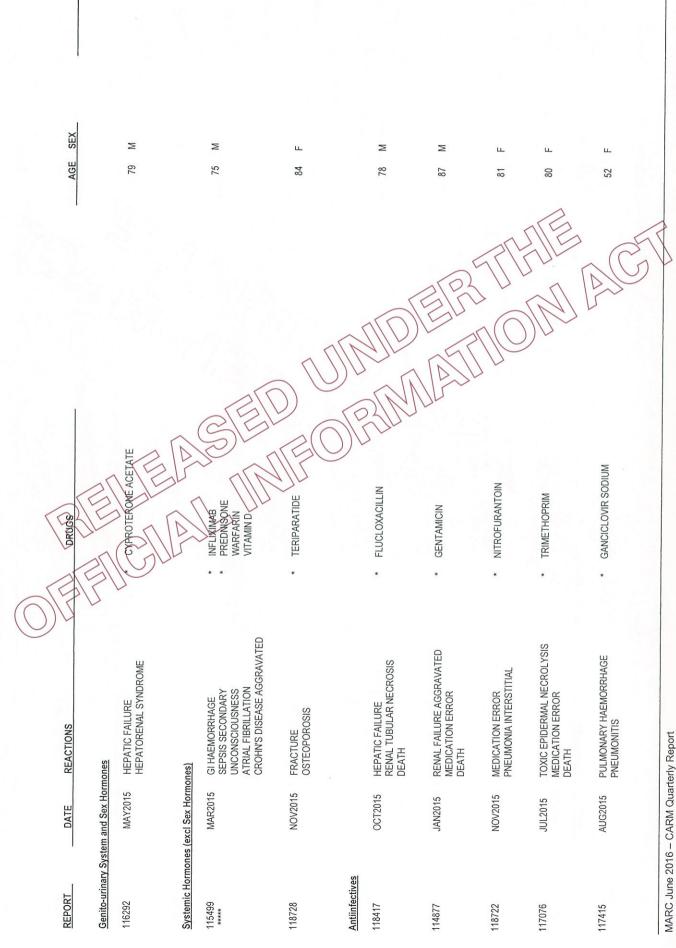
Age Group	Female	Male	Unknown	Total
Under 2	2	3		5
02 - 09				
10 – 19		2		2
20 – 29		1		1
30 – 39	2	3		5
40 - 49	6	6		12
50 – 59	10	8		18
60 – 69	10	22		32
70 – 79	18	21		39
80 plus	13	6		19
Unknown		3		3
Total	61	75		136
	45%	55%		

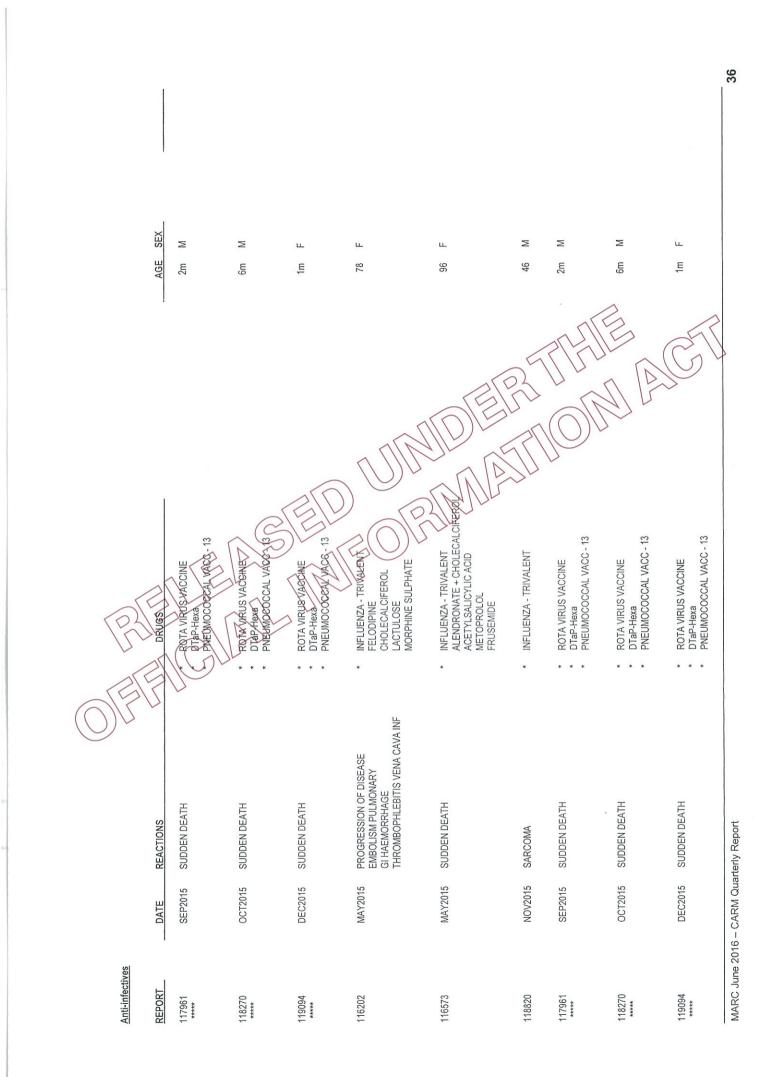
	appearing in more sality.												31
	classification and those cases tal outcome regardless of cau	AGE SEX		LL.	80 M	78 M		74 M	85 F	77 M	61 M	69 F	70 M
	ted once in each relevant ATC edicines, which resulted in a fa	1					$\sim$	ALC		R	ON		51
	nan one suspect agent are list rts, identifying 166 suspect m				SE	L L L L L L L L L L L L L L L L L L L		3AA	M				
aer 2015	Cases where there is more th	BRUGS	200	* HAISOPROSTOL	<ul> <li>DICLOFENAC</li> <li>OMERRAZOLE</li> <li>CILAZARRIL</li> <li>FRUSEMIDE</li> <li>SIMVASTATIA</li> </ul>	* AZACITIDINE * ONDANSETRON HYDROCHUDRIDE		* APIXABAN	* APIXABAN	* DABIGATRAN	<ul> <li>DABIGATRAN</li> <li>IBUPROFEN</li> <li>BACLOFEN</li> <li>METOPROLOL</li> <li>DIGOXIN</li> </ul>	* DABIGATRAN	* DABIGATRAN * WARFARIN
Annual Report Fatal Cases January to December	Reports are grouped according to the ATC classification of the suspect agent(s). Cases where there is more than one suspect agent are listed once in each relevant ATC classification and those cases appearing in more than one ATC classification and those cases appearing in more than one ATC classification are there is the value of the ATC classification and those cases appearing in more than one ATC classification are identified with ***** below the Report Number. This listing covers the value of the ATC classification are the according to the ATC classification and those cases appearing in more than one ATC classification are identified with ***** below the Report Number. This listing covers the value of the according to the resulted in a fatal outcome regardless of causality.	REACTIONS		CONGENITAL ANOMALY NOS	HYPOTENSION RENAL FAILURE ACUTE BRADYCARDIA CARDIAC ARREST MULTIPLE ORGAN FAILURE	ABSCESS PERIANAL CONSTIPATION		CEREBRAL HAEMORRHAGE ENDOCARDITIS	CARCINOMA COLON	CARDIAC TAMPONADE DISSECTING AORTIC ANEURYSM HAEMORRHAGE INTRACRANIAL	GI HAEMORRHAGE RENAL FAILURE ACUTE DRUG LEVEL INCREASED SEPSIS DEATH	HAEMORRHAGE STROKE	THROMBUS INTRACARDIAC
al Report F	according to the ication are ident	DATE		APR2015	JUL2015	AUG2015	ing organs	FEB2015	JUL2015	JAN2015	FEB2015	FEB2015	MAR2015
Table 5: Annu	Reports are grouped than one ATC classifi	REPORT	Alimentary	115922	117072 ****	117433 *****	Blood and Blood forming organs	115333	117020	114883	115140	115340	115705 MAR2015 THROMBUS

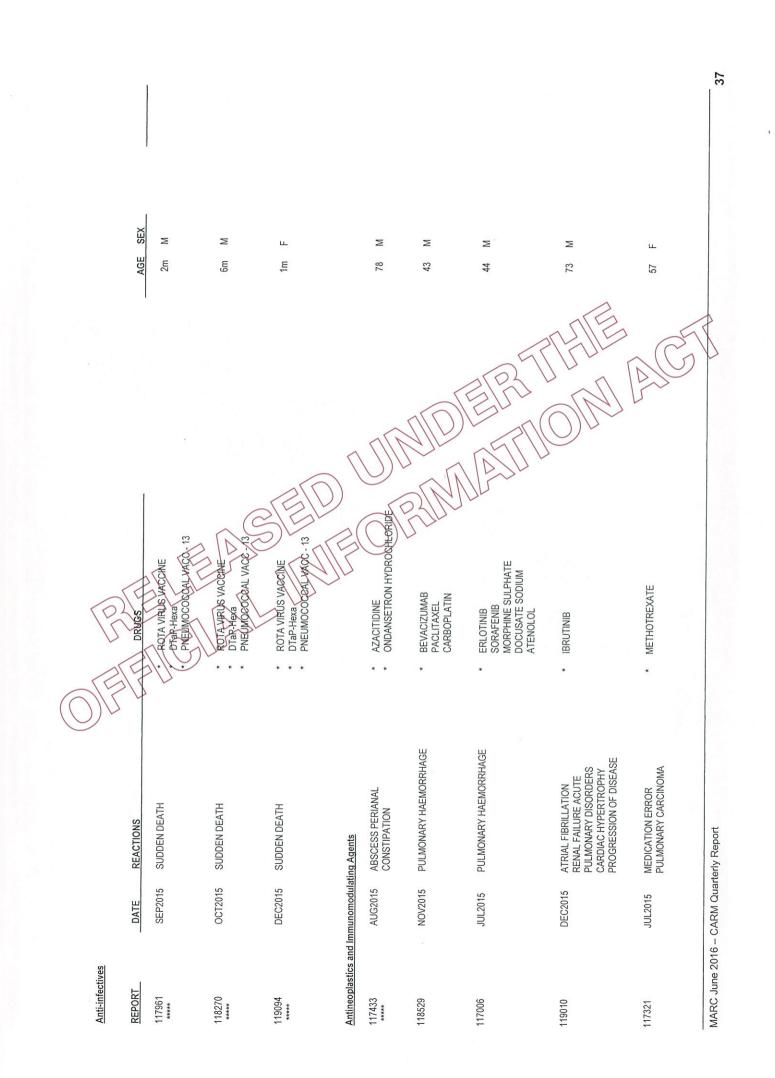




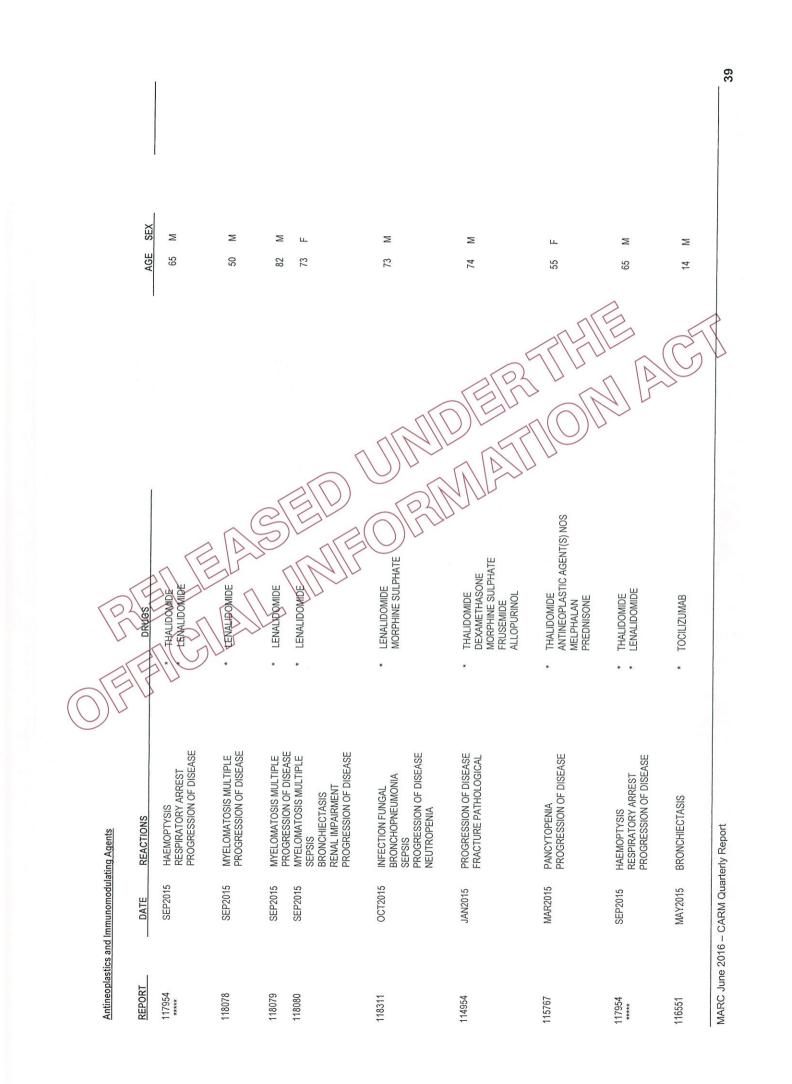


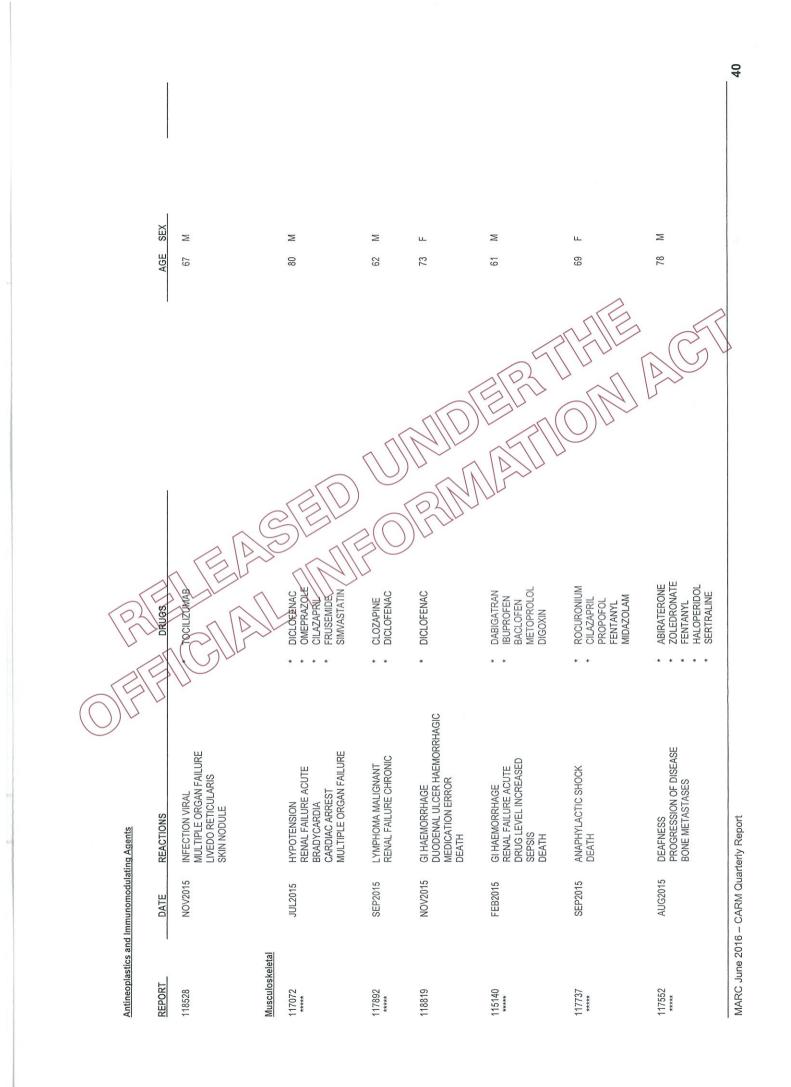


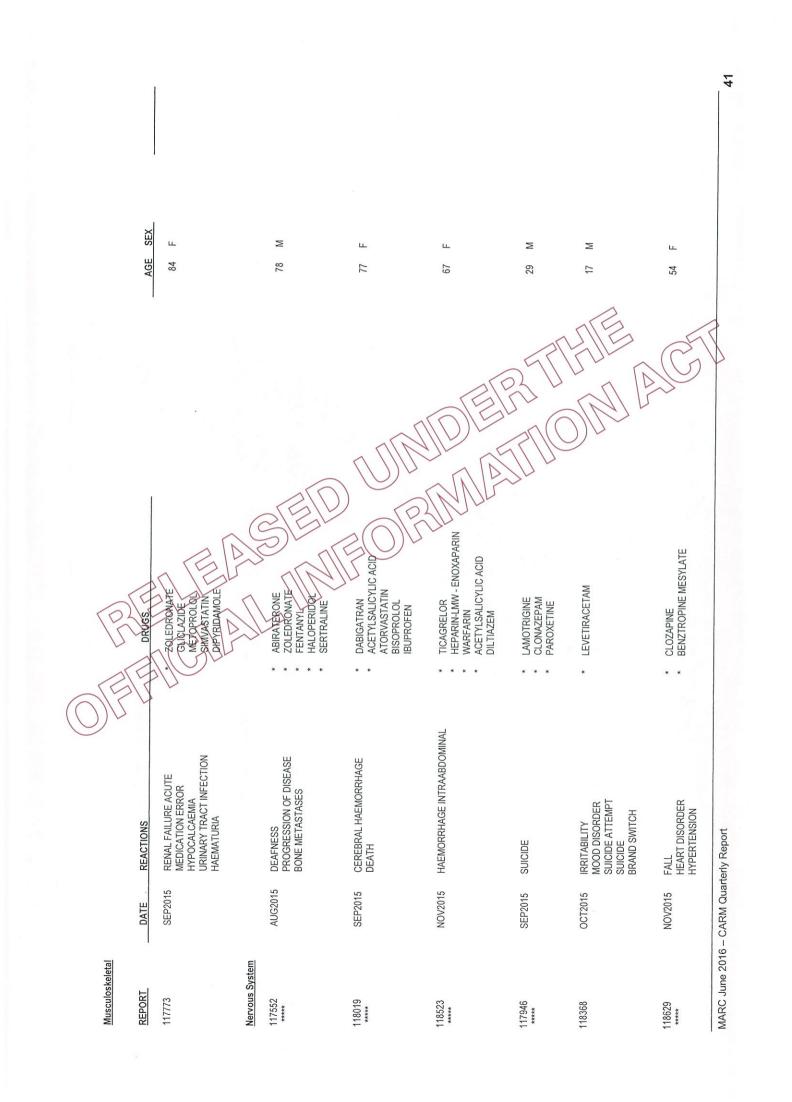


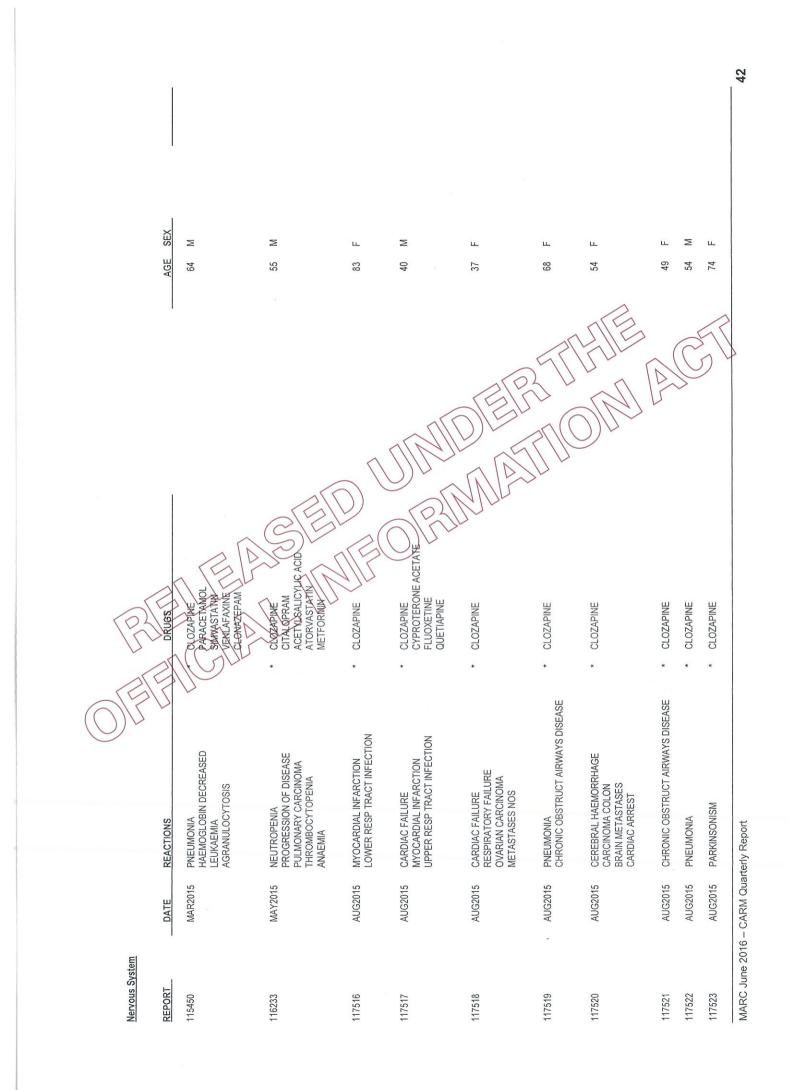


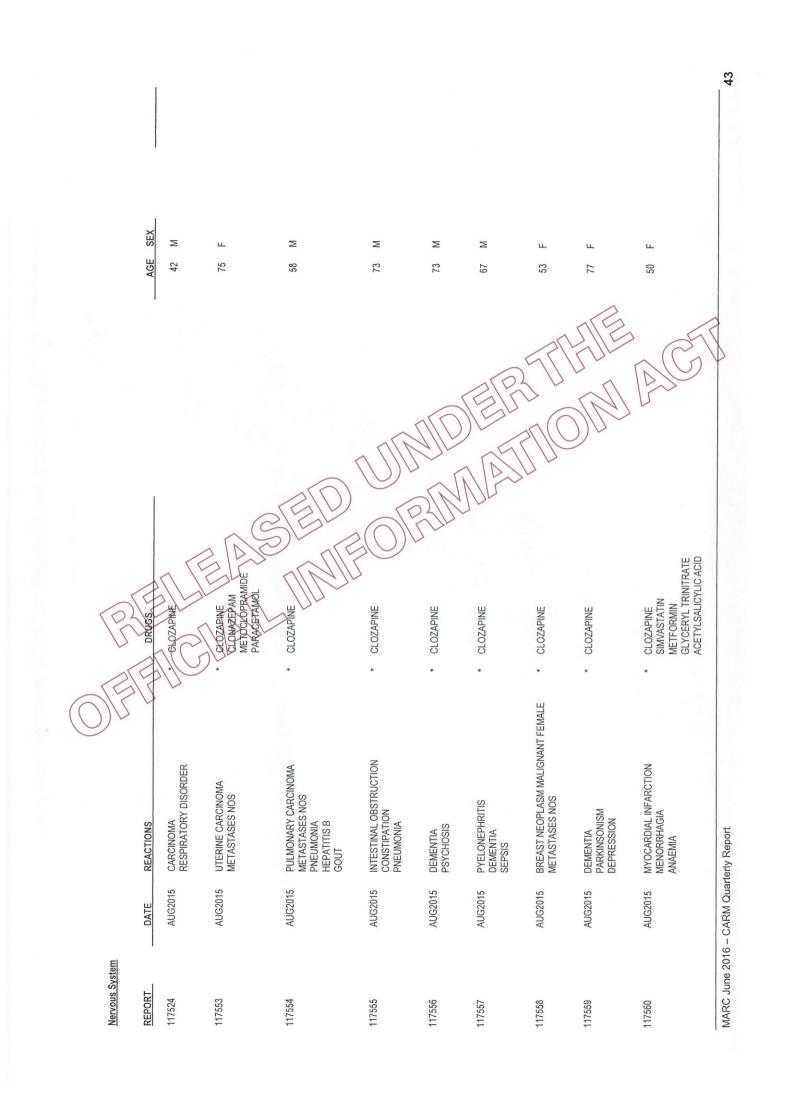
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oplastics ar	REPORT	118422	118423	118424	116486	117552 *****	115253	117245	117370	114909	115499	115622



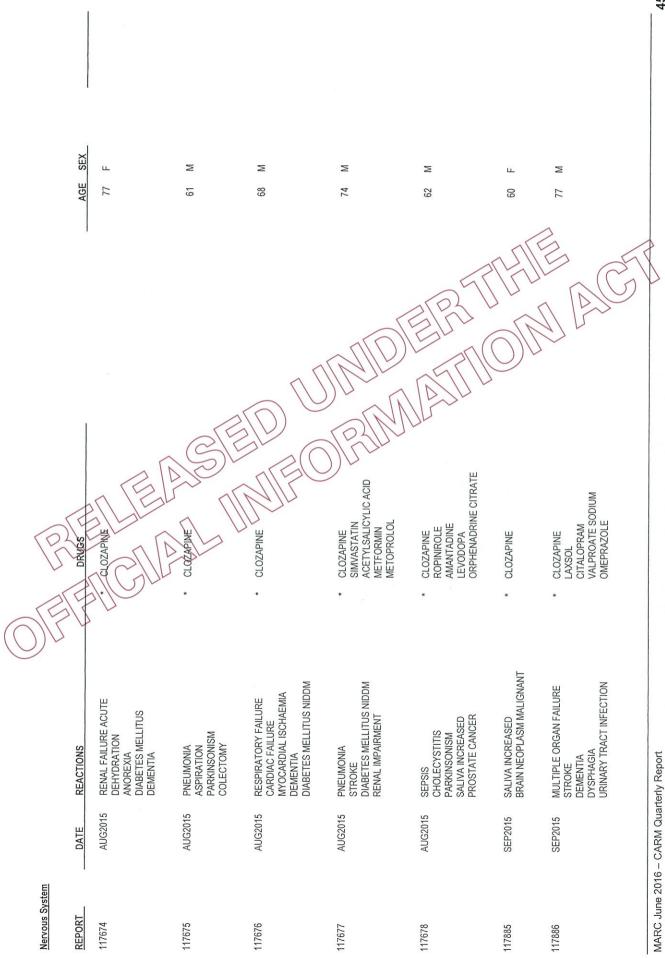


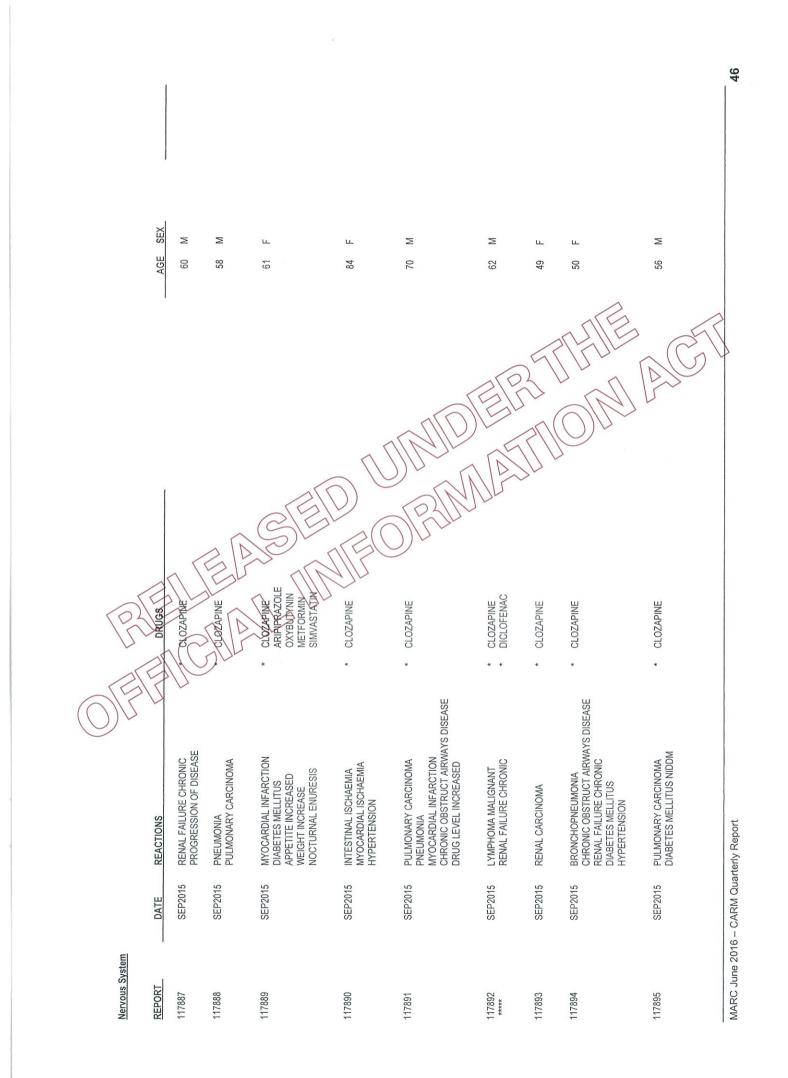




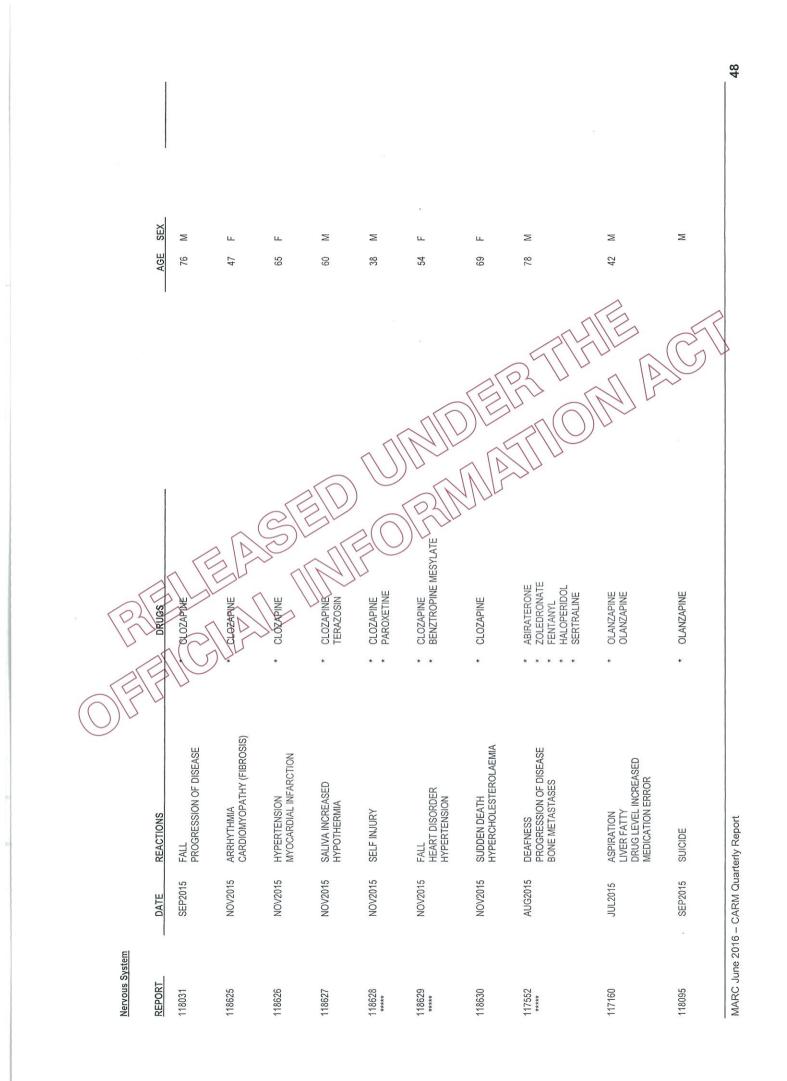


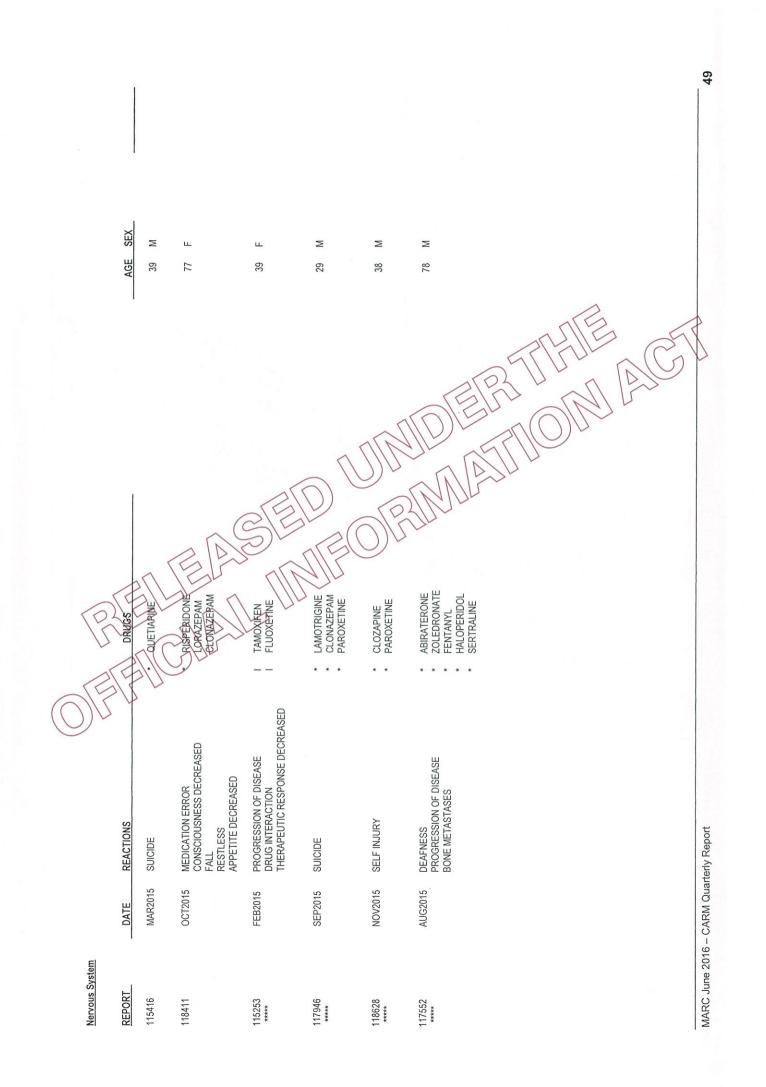
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		REACTIONS	CARDIAC ARREST DEMENTIA PNEUMONIA	PNEUMONIA DEMENTIA	CHRONIC OBSTRUCT AIRWAYS DISEASE	PULMONARY CARCINOMA BRAIN METASTASES	BREAST NEOPLASM MALIGNANT FEMALE METASTASES NOS	RENAL FAILURE ACUTE DEHYDRATION DEMENTIA INFECTION VIRAL	STROKE BRAIN METASTASES CHRONIC OBSTRUCT AIRWAYS DISEASE DIABETES MELLITUS NIDDM	PANCREAS NEOPLASM MALIGNANT METASTASES NOS STROKE HEPATITIS	MYOCARDIAL INFARCTION ATHEROSCIEROSIS DIABETES MELLITUS OBESITY	arterly Report
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	Nervous System	REPORT	117561	117562	117667	117668	117669	117670	117671	117672	117673	MARC June 2016 – CARM Quarterly Report

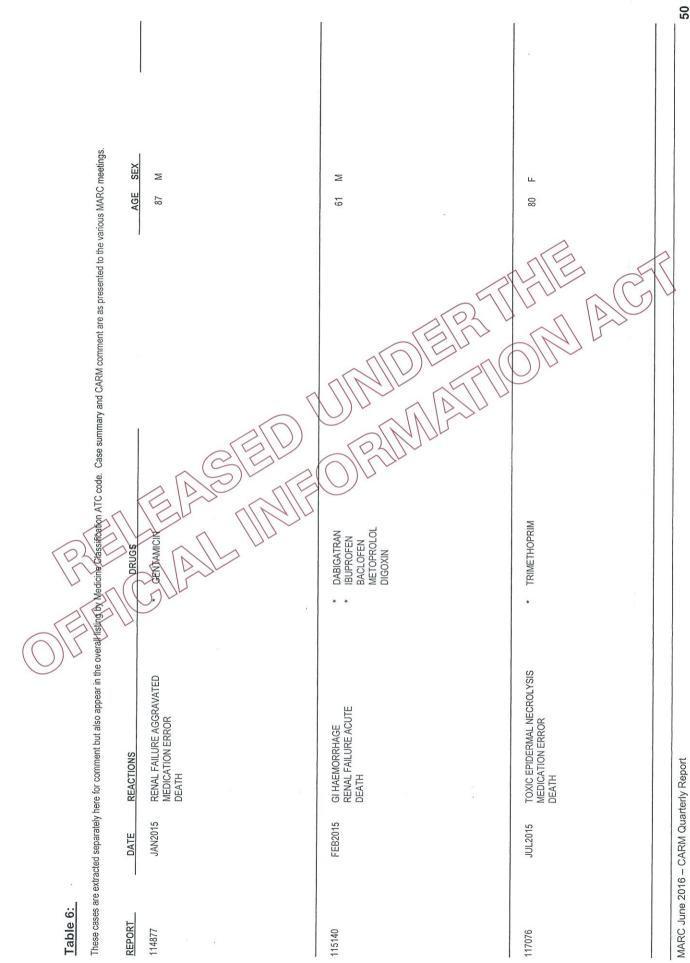




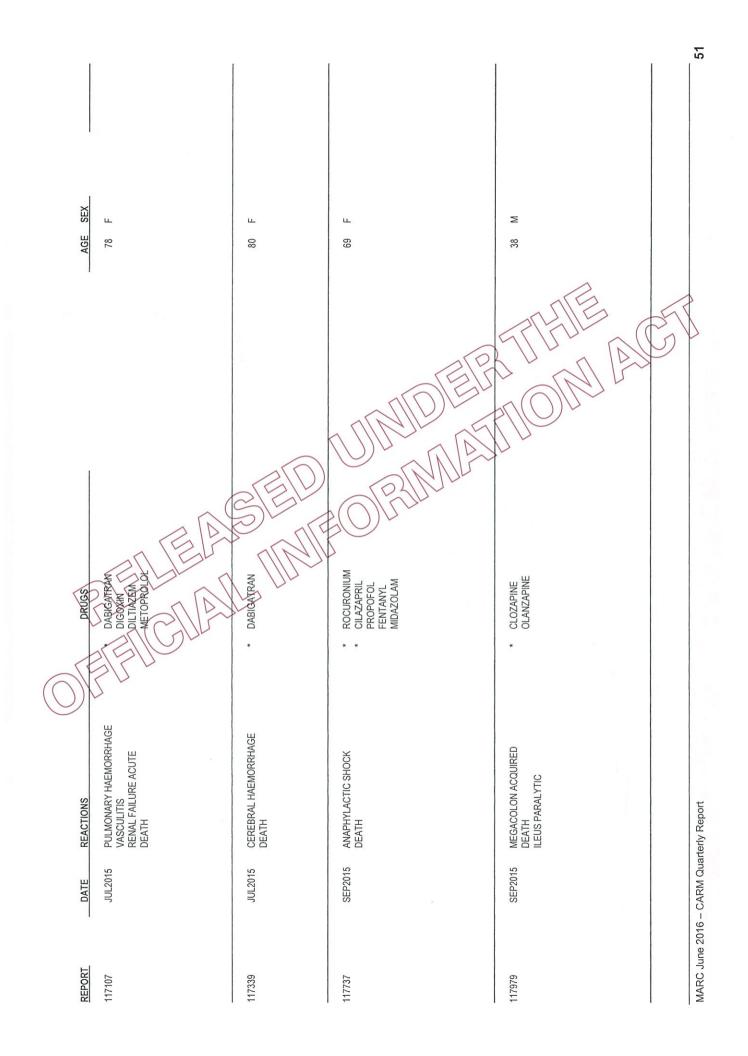
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	5	REACTIONS	STROKE PNEUMONIA	EMBOLISM PULMONARY	CARDIAC FAILURE CHRONIC OBSTRUCT AIRWAYS DISEASE	RESPIRATORY ARREST CHRONIC OBSTRUCT AIRWAYS DISEASE	STROKE MYOCARDIAL ISCHAEMIA CEREBRAL ISCHAEMIA	MEGACOLON ACQUIRED DEATH ILEUS PARALYTIC	ASPIRATION PNEUMONITIS	CEREBRAL HAEMORRHAGE ASPIRATION PNEUMONITIS PNEUMONIA	ASPIRATION PNEUMONITIS SEPSIS RESPIRATORY FAILURE MULTIPLE ORGAN FAILURE	erly Keport
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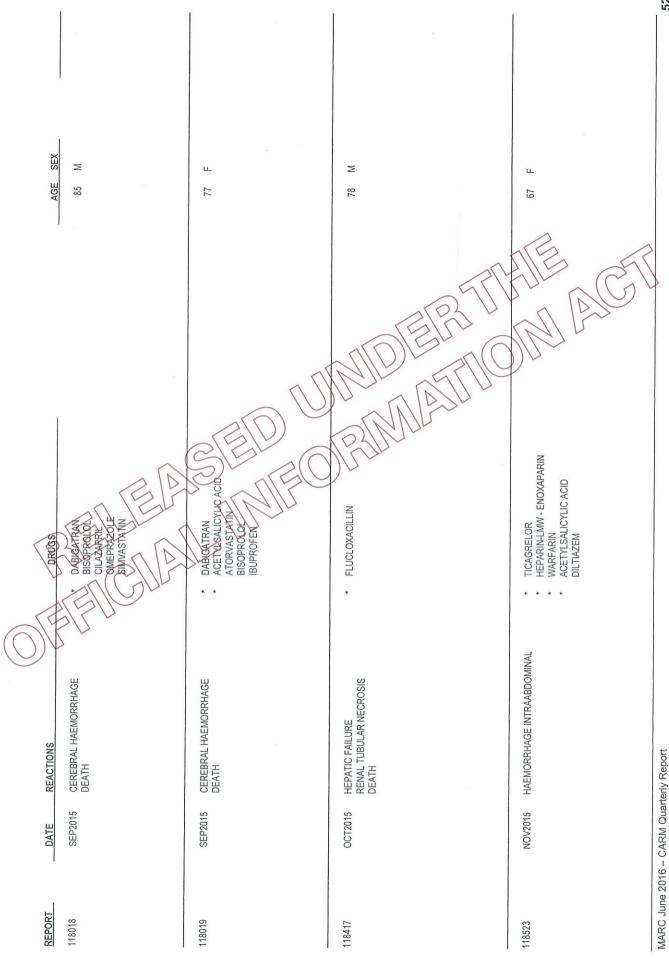


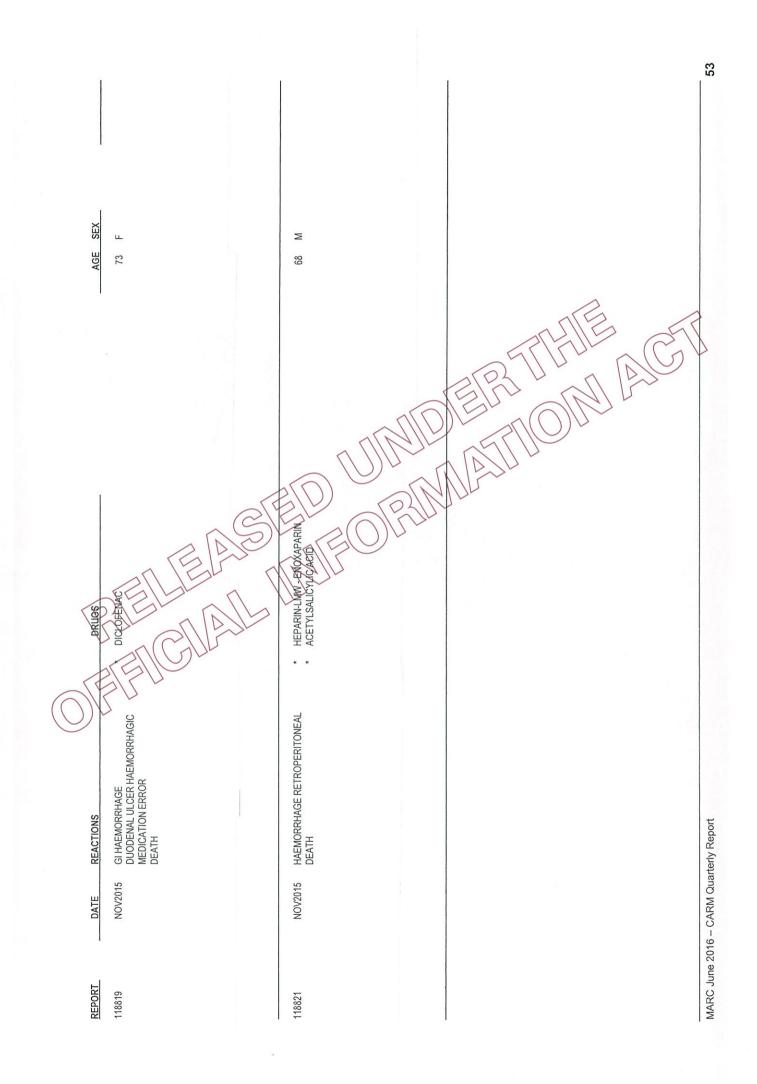




MARC June 2016 – CARM Quarterly Report







Notes:

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