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ORIGINAL ARTICLE

# Direct healthcare professional communications: A quantitative assessment study

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## Abstract

A retrospective observational study evaluated the direct healthcare professional communication (DHPC) letters disseminated by the Saudi Food and Drug Authority (SFDA) and their compliance with the pharmacovigilance guidelines. The study was utilized all DHPC letters available on the SFDA website, which is intended to communicate drug safety information to healthcare professionals (HCPs). Then, the letters were evaluated based on DHPC letter requirements approved in the European Medicines Agency (EMA) pharmacovigilance guidelines. Statistical analyses were conducted utilizing statistical analysis software (SAS® version 9.4). In June 2020, 169 letters were retrieved from the SFDA website. Most of the letters had the marketing authorization holder's logo (97%) and mentioned the date of letter issuance (98.8%). The most frequently discussed safety issues were hyperkalemia risk associated with combining renin–angiotensin–aldosterone system (RAAS) medications (10.6%) and cardiac risks (9%). Antineoplastic and immunosuppressant classes were associated with a majority of DHPC letters (15% for each category). A significant percentage of DHPC letters (10%) did not mention an agreement statement with SFDA, and 42 letters did not include marketing authorization holders (MAHs) contact information. The qualified persons responsible for pharmacovigilance and medical directors had signed most of the DHPC letters (51% and 46%, respectively). Many letters mentioned the details of reporting information to both SFDA and an MAH (82%). Moreover, 66% of the DHPC letters presented safety information within the 2-page limit. In conclusion, the DHPC letters disseminated by MAHs in Saudi Arabia have an acceptable level of compliance with the guidelines.

**KEYWORDS**
dear healthcare professional letter, pharmacovigilance, regulatory authorities, risk communications, risk minimization

## Key points

- To the best of our knowledge, this is the first study that discuss the safety concerns disseminated to healthcare providers via the DHPC letters in the Middle East.

**Abbreviations:** DHPC, direct healthcare professional communication; EMA, European Medicines Agency; HCPs, healthcare professionals; SFDA, Saudi Food and Drug Authority.

- Antineoplastic and immunosuppressant medications had remarkable numbers of safety letters.
- The most frequently discussed safety issues were related to hyperkalemia risk associated with combining RAAS system medications, cardiac risks, severe cutaneous reactions, and diabetic ketoacidosis, respectively.
- The concept of DHPC letters is not confined to adverse drug reaction; it goes beyond that to include medication error, lack of efficacy, and quality concerns.
- Regulatory authorities should carefully assess the DHPC letters based on their approved guidelines.

## 1 | INTRODUCTION

Pharmacovigilance activities at the Saudi Food and Drug Authority (SFDA) officially began in 2009. In the same year, the SFDA become a full member of the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, also known as the WHO-Uppsala Monitoring Centre.[1,2] The main role of the pharmacovigilance department is to ensure positive risk–benefit balance of drugs after marketing and to communicate important new drug safety issues to healthcare professionals. This communication informs healthcare professionals (HCPs) about certain changes in their practices to minimize patient harm and facilitate informed decision making.[3] Accordingly, the pharmacovigilance department in SFDA adopted several risk minimization measures for communicating safety information concerning the products registered within the authority.[1] These include press releases, materials in lay language for the public, a website including medicinal product information for patients and HCPs, bulletins and newsletters, and direct healthcare professional communication (DHPC) letters.[4] DHPC letters, commonly called "dear doctor letters,"[5,6] are considered the most common and preferred method of communicating safety information.[3,6,7]

Between 1980 and 2009, around 22% of drugs that were approved by Food and Drug Administration in the United States of America (US FDA) are withdrawn from the market within the first 6 years for safety reasons.[7,10] Moreover, almost 14% of registered medicinal products require DHPC letters within the first 3 years of their marketing authorization to inform HCPs about newly identified risks. Therefore, any safety concerns required actions must be communicated to HCPs to ensure patient safety.[8,9]

In the SFDA pharmacovigilance guidelines, a DHPC is defined as "a communication intervention by which important safety information is delivered directly to individual HCPs by a marketing authorization holder (MAH) or the SFDA, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product."[4]

The SFDA adopted its Good Pharmacovigilance Practices (GVP) guideline from the European guideline; there are similarity in most of the DHPC letter requirements between EMA GVP and SFDA GVP. The GVP module on safety communication (GVP XV) in EMA describes the strategies that can be used by the authorities and MAHs for communicatig of new or emerging safety information.[3] Generally, DHPC letters should be disseminated when there is a need to take immediate action or change current practice for a medicinal product. Such instances include suspension, recall, withdrawal, or revocation of a marketing authorization for safety reasons; restriction of an indication, a new contraindication, or a change in recommended dosage due to safety reasons; and a restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.[3,4] Other situations in which dissemination of a DHPC letter should be considered include new major warnings or precautions for use in the product information, new data identifying a previously unknown risk or a change in the frequency or severity of a known risk, substantiated knowledge that the medicinal product is not as effective as previously considered, new recommendations for preventing or treating adverse reactions or to avoid misuse or medication error, or ongoing assessment of a significant potential risk for which data available at a particular point in time are insufficient to take regulatory action.[3,4] Moreover, the competent authority may disseminate or request that the MAH disseminate a DHPC letter in any situation the competent authority considers necessary for the continued safe and effective use of a medicinal product.[4,5]

The preparation of DHPC letters involves cooperation between the MAH and the regulatory authority. Agreement between these two parties should be reached before a DHPC letter is issued by the MAH.[3,4] The agreement covers both the content of the information and the communication plan, including the intended recipients and the timetable for disseminating the DHPC letter.[3,4,6]

The message of the DHPC letter should be clear and concise regarding the safety concern. It is recommended to not exceed two pages.[5] Providing clear and appropriate information in the letters enhances their usability. In addition, stating the facts behind the recommendations in the letters helps HCPs take action on the recommendations.[6] The GVP XV module includes a template for DHPC letter, stating that safety concerns should be presented in context along with the benefits of the drug.[4,6] DHPC letter should further include relevant information about the safety concerns, such as severity and frequency of side effects, and explain any recommendations to HCPs and evidence supporting the recommendations.[4,6]

To our knowledge, no study has been conducted in the Middle East to discuss safety concerns disseminated to HCPs via DHPC letters, what types of medications have DHPC letters, what

characteristics these medications possess, and to what extent these DHPC letters contain structured information (e.g., title, date, main message) based on regulatory requirements. Therefore, this study aimed to qualitatively and quantitatively evaluate the DHPC letters submitted to the SFDA by MAHs.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

A retrospective observational study was utilized to review the available DHPC letters intended to communicate important new drug safety information to HCPs on the SFDA website (www.sfda.gov.sa). The study was conducted between December 2019 and June 2020. All DHPC letters that were available on the website were reviewed in this study. During the study period, the first letter was published in 2011, and the most recent one had been published in April 2020.

### 2.2 | Data collection and analysis

Two independent reviewers reviewed the letters. A specific data collection form was created to evaluate the letters based on DHPC requirements approved in the European pharmacovigilance guidelines. The main elements included were the date of letter issuance, MAH name, MAH logo, letter title, trade and generic names of the product of interest, summary (including reason for letter dissemination and brief description of safety concerns), recommendations for risk minimization (e.g., contraindications, warnings, precautions for use, and alternative treatment), and recall information including pharmacy or patient level and date of recall (if applicable). Moreover, we noted the presence of an SFDA agreement statement—a statement indicating that the information had been sent in agreement with the national medicines authority. Further information on the safety concerns and recommendations including adverse reaction, severity, statement on the suspected causal relationship, the estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure, presence of a statement indicating any association between the adverse reaction and off-label use, and details on the recommendations for risk minimization were noted. In addition, links or references to other relevant information and calls for reporting were noted. The calls for reporting are reminders of the need to report and how to report adverse reactions in accordance with the national spontaneous reporting system. They contained details on how to access the national spontaneous reporting system to MAH and SFDA (e.g., names, postal addresses, fax numbers, website addresses) and similar point-of-contact information for MAH. Finally, we recorded the number of pages for each DHPC letter, signature availability, and by whom the letters had been signed. Each letter was assessed based on all the elements listed above. Descriptive statistics were performed on the retrieved letters to accurately interpret and present the results. Statistical analyses were conducted using statistical analysis software (SAS® version 9.4).

## 3 | RESULTS

One hundred sixty-nine letters were retrieved from the SFDA website in June 2020 (Table 1). The first letter was published in October 2011, and the most recent letter had been published in April 2020. Most of the letters bore their MAH's logo (*n* = 164; 97%) and mentioned the date of letter issuance (*n* = 167; 98.8%). Regarding medication name, four letters (2%) did not mention the trade name, and one letter (0.6%) did not mention the generic name of the medicinal product of interest. In regard to safety concerns, the most frequently discussed safety issues were hyperkalemia risk that is related to combining RAAS system medications (*n* = 18; 10.6%), cardiac risks (*n* = 15; 9%), severe cutaneous reactions (*n* = 7; 4%), and diabetic ketoacidosis (*n* = 3; 1.8%); respectively.

Approximately 17% and 16% of the letters were disseminated in 2014 and 2015, respectively (Table 2). In 2014, 28 letters were disseminated. Of these, nine letters dealt with the restriction of combined RAAS medications, and seven letters contained recommendations to minimize cardiac risks. Twenty-six letters were distributed in 2015. Of them, six letters were related to hyperkalemia risk that are related to combining RAAS system medications and two letters were related to the risk of thrombotic microangiopathy with interferon beta products.

Concerning medication classes, it was found that antineoplastic and immunosuppressant classes were associated with a majority of DHPC letters, with 26 letters (15%) each. Some antineoplastic agents commonly associated with the safety letters include atezolizumab, dasatinib, rituximaband, and vemurafenib (Table 3). For immunosuppressants, we found letters for fingolimod, mycophenolate mofetil, and other agents (Table 4).

More elements were assessed during the study. These included the availability of recall information, risk–benefit information, clinical evidence, and list of literature references. Twenty-one letters (12%) included information about the benefits and risks of using the product, 101 letters (60%) included clinical evidence, 18 letters (10.6%) included lists of literature references, three letters (1.7%) included recall information and one letter includes withdrawn information. The recall letters include recalling of Cilest® (norgestimate) tablets due to the out-of-specification result of dissolution testing, recalling of Augmentin® infant drop formulation that included incorrect dosing information in the patient leaflet and recalling of Viread® (tenofovir) tablets due to the possible presence of silicone rubber. The withdrawn letter was for Miacalcic® (calcitonin) nasal due to increased risk of malignancies with long-term calcitonin use compared with placebo-treated patients. A significant percentage of the letters (*n* = 17; 10%) did not mention any agreement statement with SFDA, and 42 letters (25%) did not include any MAH contact information. In place of the reporting statement, many letters mentioned the details

**TABLE 1** List of the medications (*N* = 169) and their trade and generic names, their class, and the associated adverse events in the DHCP letters that were retrieved from the FDA website till June 2020

| Trade name | Generic name | Medication class | Adverse events |
|---|---|---|---|
| 1. Depakine | Valproate | Antiepileptic | Abnormal pregnancy outcomes |
| 2. Depakine | Valproate | Antiepileptic | Abnormal pregnancy outcomes |
| 3. Imnovid/Pomalyst | Pomalidomide | Immunosuppressant | Risk of hepatotoxicity, interstitial lung disease, & heart failure |
| 4. Myfortic | Mycophenolate mofetil | Immunosuppressant | Amended recommendations for contraception |
| 5. Cellcept | Mycophenolate mofetil | Immunosuppressant | Amended recommendations for contraception |
| 6. Tasigna | Nilotinib | Antineoplastic | Atherosclerosis |
| 7. Xarelto | Rivaroxaban | Antithrombotic agent | Awareness of safety profile |
| 8. Actemra | Tocilizumab | Immunosuppressant | Awareness of safety profile |
| 9. Actos | Pioglitazone | Blood glucose lowering | Bladder cancer |
| 10. Plavix | Clopidogrel | Antithrombotic agent | Bleeding in atrial fibrillation patients |
| 11. Sovaldi, Harvoni | Sofosbuvir, sofosbuvir, & ledipasvir | Antivirals | Bradycardia |
| 12. Neupogen, Neulasta | Filgrastim, pegfilgrastim | Immunostimulants | Capillary leak syndrome |
| 13. Gilenya | Fingolimod | Immunosuppressant | Cardiovascular adverse drug reactionafter first dose |
| 14. Epifenac | Diclofenac | Antiinflammatory & antirheumatic products, nonsteroidal | Cardiovascular risk |
| 15. Diclomax, Oflan | Diclofenac | Antiinflammatory & antirheumatic products, nonsteroidal | Cardiovascular risk |
| 16. Not applicable | Diclofenac | Antiinflammatory & antirheumatic products, nonsteroidal | Cardiovascular risk |
| 17. Rofenac | Diclofenac | Antiinflammatory & antirheumatic products, nonsteroidal | Cardiovascular risk |
| 18. Yasmin | Ethinylestradiol/ drospirenone | Contraceptive | Change in labelling information |
| 19. Tiapridal | Tiapride | Antipsychotic | Change in labelling information |
| 20. Aclasta | Not applicable. | Bone structure & mineralization | Contraindication |
| 21. Solu-Medrol | Methylprednisolone | Corticosteroid | Contraindication |
| 22. Fegona | Fingolimod | Immunosuppressant | Contraindication in patients with cardiac conditions |
| 23. Gilenya | Fingolimod | Immunosuppressant | Contraindication in patients with cardiac conditions |
| 24. Benlysta | Belimumab | Immunosuppressant | Depression and/or suicidal ideation |
| 25. Forxiga, Xigduo XR | Dapagliflozin, SGLT–2 inhibitor | Blood glucose lowering | Diabetic ketoacidosis |
| 26. Jardiance, Synjardy | Sglt2i (empagliflizin, empagliflizin, metformin) | Blood glucose lowering | Diabetic ketoacidosis |
| 27. Invokana, Vokanamet | Canagliflozin, canagliflozin/ metformin | Blood glucose lowering | Diabetic ketoacidosis |
| 28. Soliqua | Glargine/lixisenatide | Blood glucose lowering | Dosing |
| 29. Clexane | Enoxaparin | Antithrombotic agent | Dosing in renal impairment |
| 30. Zelboraf | Vemurafenib | Antineoplastic | Dupuytren's contracture & facial fibromatosis |
| 31. Benlysta | Belimumab | Immunosuppressant | Fatal cases of progressive multifocal leukoencephalopathy in systemic lupus erythematosus patients |
| 32. Forxiga, Xigduo XR | Dapagliflozin, Sglt3 | Blood glucose lowering | Fournier's gangrene |

(Continues)

TABLE 1 (Continued)

| Trade name | Generic name | Medication class | Adverse events |
|---|---|---|---|
| 33. Jardiance, Synjardy | Sglt2i (empagliflizin, empagliflizin/metformin) | Blood glucose lowering | Fournier's gangrene |
| 34. Invokana | Canagliflozin, Sglt2i | Blood glucose lowering | Fournier's gangrene |
| 35. Pradaxa | Dabigatran etexilate | Antithrombotic agent | Gastrointestinal bleeding |
| 36. Glevic, Tasigna | Imatinib, nilotinib | Antineoplastic | Hepatitis B reactivation |
| 37. Mabthera | Rituximab | Antineoplastic | Hepatitis B reactivation |
| 38. Darzalex | Daratumumab | Antineoplastic | Hepatitis B reactivation |
| 39. Arzerra | Ofatumumab | Antineoplastic | Hepatitis B reactivation |
| 40. Sprycel | Dasatinib | Antineoplastic | Hepatitis B reactivation |
| 41. Actermra | Tocilizumab | Immunosuppressant | Hepatotoxicity |
| 42. Xalkori | Crizotinib | Antineoplastic | Heart failure |
| 43. Adenuric | Febuxostat | Antigout preparation | Higher rate of cardiovascular death in gout patients with cardiovascular disease |
| 44. Gilenya | Fingolimod | Immunosuppressant | HPS |
| 45. Ultravist | Iopromide | Low osmolar X-ray contrast medium | Hypersensitivity |
| 46. Resperdal, Resperdal Consta, Invega | Resperidone, paliperidone | Antipsychotics | Intraoperative floppy iris syndrome |
| 47. Ridon | Risperidone | Antipsychotic | Intraoperative floppy iris syndrome |
| 48. Votrient | Pazopanib | Antineoplastic | Important change to frequency of serum liver test monitoring for hepatotoxicity |
| 49. Augmentin | Amoxicillin/clavulanic acid | Antibacterial | Recall/Incorrect information in patient information leaflet |
| 50. Wellbutrin, Zyban | Bupropion | Antidepressant | Increased congenital cardiovascular malformations |
| 51. Tygacil | Tigecycline | Antibacterial | Increase in mortality |
| 52. Ribomustib | Bendamustine | Antineoplastic | Increased mortality in recent clinical studies |
| 53. Not applicable. | Azithromycin | Antibacterial | Increased rate of relapses of hematological malignancies & mortality in HSCT |
| 54. Protelos | Strontium ranelate | Drugs affecting bone structure & mineralization | Increased risk of myocardial infarction |
| 55. Not applicable | Darunavir, cobicistat | Antivirals | Increased risk of treatment failure & increased risk of mother-to-child transmission of HIV infection due to lower exposure of drunavir & cobicistat during the second & third trimesters of pregnancy |
| 56. Gencoya, Stribild | Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide/disoproxil | Antivirals | Increased risk of treatment failure & increased risk of mother-to-child transmission of HIV infection due to lower exposure of elvitegravir & cobicistat during the second & third trimesters of pregnancy |
| 57. Cosmofer | Low molecular wt. iron dextran | Supplement | Indication & administration |
| 58. Stelara | Ustekinumab | Immunosuppressant | Infections, reversible posterior leukoencephalopathy syndrome, skin conditions |
| 59. Arzerra | Ofatumumab | Antineoplastic | Infusion reaction in chronic lymphocytic leukemia patients |
| 60. Calmtrol | Risperidone | Antipsychotic | Intraoperative floppy iris syndrome in patients undergoing cataract surgery & taking Calmtrol 0.5, 1, 2, 3, or 4-mg. |

(Continues)

TABLE 1 (Continued)

| Trade name | Generic name | Medication class | Adverse events |
|---|---|---|---|
| 61. Navidoxine | Meclozin hydrochloric acid /pyridoxine hydrochloric acid | Antihistamines | Labelling deficiencies |
| 62. Eligard | Leuprorelin acetate depot injection | Gonadotropin releasing hormone analogue | Lack of efficacy |
| 63. Voldoxan | Agomelatine | Antidepressant | Liver function monitoring |
| 64. Zelboral | Vemurafenib | Antineoplastic | Liver injury |
| 65. Invokana, Vokanamet | Canagliflozin, canagliflozin/ metformin | Blood glucose lowering | Lower limb amputation |
| 66. Keppra | Levetiracetam | Antiepileptic | Medication error |
| 67. Jectin−12 | Cyanocobalamin | Vitamin B12 (cyanocobalamin & analogues) | Medication error |
| 68. Abelcet, Ambisom, Fungizone | Amphotericin B | Antiinfective | Medication error with parenteral formulation |
| 69. Blincyto | Blinatumomab | Antineoplastic | Medication error |
| 70. Tresiba | Degludec | Blood glucose lowering | Mixing up to strength |
| 71. Xgeva | Denosumab | Drugs affecting bone structure & mineralization | Vertebral compression fracture following discontinuation |
| 72. Tecentriq | Atezolizumab | Antineoplastic | Myocarditis |
| 73. Tecentriq | Atezolizumab | Antineoplastic | Myositis |
| 74. Avastin | Bevacizumab | Antineoplastic | Necrotizing fasciitis |
| 75. Tecentriq | Atezolizumab | Antineoplastic | Nephritis |
| 76. Tivicay, Tirumeq | Dolutegravir, abacavir, lamivudine | Antivirals | Neural tube defects |
| 77. Roaccutane | Isotretinoin | Antiacne preparation, topical | Neuropsychiatric |
| 78. Adempas | Riociguat | Antihypertensive | New contraindication regarding pulmonary hypertension with pulmonary hypertension—idiopathic interstitial pneumonia |
| 79. Gilenya | Fingolimod | Immunosuppressant | New contraindication in pregnant women & in women of childbearing potential not using effective contraception |
| 80. Amistop | Domperidone | Propulsive | New recommendation to minimize cardiac risks |
| 81. Motilium | Domperidone | Propulsive | New recommendation to minimize cardiac risks |
| 82. Mododom | Domperidone | Propulsive | New recommendation to minimize cardiac risks |
| 83. Prokinin | Domperidone | Propulsive | New recommendation to minimize cardiac risks |
| 84. Xofigo | Radium 223 dichloride | Radiopharmaceutical | New restrictions on use due to increased risk of fracture & trend for increased mortality |
| 85. Lemtrada | Alemtuzumab | Immunosuppressant | New safety information |
| 86. Durogesic | Fentanyl | Opioid | Serotonin syndrome under coadministration with serotonergic drugs |
| 87. Fentanyl (Janssen) | Fentanyl | Opioid | Serotonin syndrome under coadministration with serotonergic drugs |
| 88. Simulect | Basiliximab | Immunosuppressant | Off-label use |
| 89. Prolia | Denosumab | Drugs affecting bone structure & mineralization | Osteonecrosis of jaw, hypocalcemia, atypical femoral fracture |
| 90. Forteo | Teriparatide | Parathyroid hormones & analogues | Osteosarcoma |
| 91. Sprycel | Dasatinib | Antineoplastic | Pulmonary arterial hypertension |

(Continues)

TABLE 1 (Continued)

| Trade name | Generic name | Medication class | Adverse events |
|---|---|---|---|
| 92. Propecia, Proscar | Finasteride | Testosterone-5-alpha reductase inhibitors | Psychiatric disorder & sexual dysfunction |
| 93. Tysabri | Natalizumab | Immunosuppressant | Progressive multifocal leukoencephalopathy |
| 94. Gilenya | Fingolimod | Immunosuppressant | Progressive multifocal leukoencephalopathy |
| 95. Zofran | Ondansetron | Antiemetic & antinauseant | Posology of intravenous use & dose-dependent QT prolongation |
| 96. Curacne | Isotretinoin | Antiacne preparation, topical | Pregnancy prevention program |
| 97. Roaccutane | Isotretinoin | Antiacne preparation, topical | Pregnancy prevention program |
| 98. Concetra | Methylphenidate hydrochloric acid | Psychostimulant | Priapism |
| 99. Xgeva | Denosumab | Drugs affecting bone structure & mineralization | Primary malignancy |
| 100. Xeljanz | Tofacitinib | Immunosuppressant | Pulmonary embolism & overall mortality |
| 101. Kytril | Granisetron hydrochloric acid | Antiemetic & antinauseant | QT prolongation |
| 102. Zelboral | Vemurafenib | Antineoplastic | Radiation toxicity |
| 103. Viread | Tenofovir | Antiviral | Recall |
| 104. Cilest | Norgestimate | Contraceptive | Recall |
| 105. Tekam, Hikma Midazolam, Floran | Ketamine, midazolam, isoflurane | Anesthetics, general | Recommendation for indication |
| 106. Not applicable. | Apixaban, edocaban, dabigatran, rivaroxaban | Antithrombotic agents | Recommendation for indication |
| 107. Vastarel | Trimetazidine | Cardiac therapy | Reevaluation outcome |
| 108. Procoralan | Ivabradine | Cardiac therapy | Reminder about ivabradine indications |
| 109. Herceptin | Trastuzumab | Antineoplastic | Reminder of cardiac monitoring |
| 110. Procoralan | Ivabradine | Cardiac therapy | Reregistration |
| 111. Mencevax ACWY | Meningococcal groups A, C, W135, Y | Vaccine | Resistance |
| 112. Atacand, Zesrtil | Lisinopril, candesartan, cilexetil | Antihypertensives | Restriction of combined RAAS medicine |
| 113. Micardis, Micardis Plus | Telmisartan, telmisartan hydrochloric acid | Antihypertensives | Restriction of combined RAAS medicine |
| 114. Angiotec | Enalapril | Antihypertensive | Restriction of combined RAAS medicine |
| 115. Lacine | Losartan | Antihypertensive | Restriction of combined RAAS medicine |
| 116. Arena | Irbesartan | Antihypertensive | Restriction of combined RAAS medicine |
| 117. Zinopril | Lisinopril | Antihypertensive | Restriction of combined RAAS medicine |
| 118. Cozar, Hyzaar, Fortzaar, Co-Renitec, Renitec | Losartan K, enalapril maleate | Antihypertensives | Restriction of combined RAAS medicine |
| 119. Diovan, Exforge, Exforge HTC, Co-Diovan, Rasilez HTC | Valsartan, aliskiren | Antihypertensives | Restriction of combined RAAS medicine |
| 120. Amlor Plus | Valsartan | Antihypertensive | Restriction of combined RAAS medicine |
| 121. Acuitel | Quinapril | Antihypertensive | Restriction of combined RAAS medicine |
| 122. Valtense Plus | Valsartan | Antihypertensive | Restriction of combined RAAS medicine |
| 123. Korandik | Enalapril | Antihypertensive | Restriction of combined RAAS medicine |
| 124. Lisorill | Lisinopril | Antihypertensive | Restriction of combined RAAS medicine |
| 125. Riapril | Enalapril | Antihypertensive | Restriction of combined RAAS medicine |

(Continues)

TABLE 1 (Continued)

| Trade name | Generic name | Medication class | Adverse events |
|---|---|---|---|
| 126. Aprovel, Coaprovel | Irbesartan, irbesartan/hydrochlorothiazide | Antihypertensives | Restriction of combined RAAS medicine |
| 127. Coversyl, Preterax, Bi-Preterax, Coveram | Perindopril arginine | Antihypertensives | Restriction of combined RAAS medicine |
| 128. Sortiva | Losartan | Antihypertensive | Restriction of combined RAAS medicine |
| 129. Keytruda | Pembrolizumab | Antineoplastic | Restriction of indication |
| 130. Arcoxia | Etoricoxib | Antiinflammatory & antirheumatic, nonsteroidal | Revised dose for rheumatoid arthritis or ankylosing spondylitis |
| 131. Tecentriq | Atezolizumab | Antineoplastic | Revision of indication |
| 132. Advaquin | Levofloxacin | Antibacterial | Risk of aneurysm & dissection |
| 133. Optimark, Dotarem | Gadoversetamide, gadoterate | Magnetic Resonance Imaging Contrast Media | Risk of brain deposits associated with repeated use of gadolinium-based contrast agents in magnetic resonance imaging |
| 134. Jadenu | Deferasirox | Iron chelating agent | Risk of medication error |
| 135. Arava | Leflunomide | Immunosuppressant | Risks of hepatic reactions & teratogenicity, & contraindications |
| 136. Gilenya | Fingolimod | Immunosuppressant | Risks related to immune system |
| 137. Fegona | Fingolimod | Immunosuppressant | Risks related to immune system |
| 138. Lariam | Mefloquine | Antimalarial | Safety update regarding visual disturbance |
| 139. Carvidol | Carvedilol | Antihypertensive | Scarring |
| 140. Blincyto | Blinatumomab | Antineoplastic | Serious risk |
| 141. Reminyl | Galantaamine hydrobromide | Alzheimer's disease | Severe cutaneous reaction |
| 142. Eprex | Epoetin alfa | Antianemic | Severe cutaneous reaction |
| 143. Binocrit | Epoetin alfa | Antianemic | Severe cutaneous reaction |
| 144. Recormon, Mircera | Epoetin alfa | Antianemic | Severe cutaneous reaction |
| 145. Avastin | Bevacizumab | Antineoplastic | Severe endophthalmitis |
| 146. Aranesp | Darbepoetin | Antianemic | Severe cutaneous reaction |
| 147. Xarelto | Rivaroxaban | Antithrombotic agent | Stevens–Johnson syndrome & agranulocytosis |
| 148. Mabthera | Rituximab | Antineoplastic | Stevens–Johnson syndrome & toxic epidermal necrolysis |
| 149. Levera | Daclatasvir | Antiviral | Tachycardia |
| 150. Vectibix | Panitumumab | Antineoplastic | Toxic epidermal necrolysis |
| 151. Cellcept | Mycophenolate mofetil | Immunosuppressant | Teratogenic risk, new pregnancy prevention for males & females |
| 152. Myora | Mycophenolate mofetil | Immunosuppressant | Teratogenicity |
| 153. Solpadeine | Codeine | Cough suppressant, excluding combinations with expectorants | Use of codeine-containing products for children after tonsillectomy or adenoidectomy |
| 154. Diane 35 | Ethinylestradiol/cyproterone | Contraceptives | Thromboembolism |
| 155. Betaferon | Interferon beta products | Immunostimulant | Thrombotic microangiopathy & nephrotic syndrome |
| 156. Rebif | Interferon beta | Immunostimulant | Thrombotic microangiopathy & nephrotic syndrome |
| 157. Saxenda | Liraglutide | Blood glucose lowering | Thyroid C-cell tumor & acute pancreatitis |
| 158. Xofigo | Radium 223 dichloride | Radiopharmaceutical | Update regarding increase death & fractures in randomized controlled trial |
| 159. Revlimid | Lenalidomide | Immunosuppressant | Viral reactivation |
| 160. Topamax | Topiramate | Antiepileptic | Visual field defect risk with use of Topamax |

(Continues)

TABLE 1 (Continued)

| Trade name | Generic name | Medication class | Adverse events |
|---|---|---|---|
| 161. Miacalcic | Calcitonin | Anti-parathyroid agent | Withdrawal |
| 162. Kyprolis | Carfilzomib | Antineoplastic | Risk of progressive multifocal leukoencephalopathy & hepatitis B reactivation |
| 163. Olmepress | Ondansetron | Antiemetic & antinauseant | Restriction of combined RAAS medicine |
| 164. Zofran | Ondansetron | Antiemetics & Antinauseants | Risk of birth defects |
| 165. Xeljanz | Tofacitinib | Immunosuppressant | Increased risk of venous thromboembolism, increased risk of serious & fatal infections |
| 166. Ecalta | Anidulafungin | Antiinfective | Solution for infusion must no longer be frozen |
| 167. Esbriet | Pirfenidone | Immunosuppressant | Drug-induced liver injury |
| 168. Fegona | Fingolimod | Immunosuppressant | New contraindications in pregnant women & in women of childbearing potential not using effective contraception |
| 169. Ebewe | Methotrexate | Antineoplastic | Potentially fatal dosing errors when used for autoimmune diseases |

**TABLE 2** Annual distribution of the 169 DHPC letters in SFDA

| Year | Number of DHPC letters (%) |
|---|---|
| 2011 | 5 (3%) |
| 2012 | 4 (2.4%) |
| 2013 | 22 (13.6%) |
| 2014 | 28 (17%) |
| 2015 | 26 (16%) |
| 2016 | 18 (11%) |
| 2017 | 17 (10.5%) |
| 2018 | 22 (13.6%) |
| 2019 | 21 (12.4%) |
| 2020 | 3 (1.8%) |
| No date | 3 (1.8%) |
| Total | 169 |

**TABLE 3** Letters associated with antineoplastic agents

| Trade name | Generic name | Number of letters |
|---|---|---|
| Tecentriq | Atezolizumab | 4 |
| Zelboral | Vemurafenib | 3 |
| Sprycel | Dasatinib | 2 |
| Avastin | Bevacizumab | 2 |
| Blincyto | Blinatumomab | 2 |
| Mabthera | Rituximab | 2 |
| Arzerra | Ofatumumab | 2 |
| Xalkori | Crizotinib | 1 |
| Darzalex | Daratumumab | 1 |
| Glevic, Tasigna | Imatinib, nilotinib | 1 |
| Kyprolis | Carfilzomib | 1 |
| Tasigna | Nilotinib | 1 |
| Vectibix | Panitumumab | 1 |
| Votrient | Pazopanib | 1 |
| Keytruda | Pembrolizumab | 1 |
| Ebewe | Methotrexate | 1 |
| Herceptin | Trastuzumab | 1 |
| Ribomustib | Bendamustine | 1 |
| Total | | 28 |

of reporting information to both SFDA and MAH ($n$ = 138 letters: 82%). On the other hand, only 28 letters (17%) mentioned reporting methods to the SFDA alone; one letter (0.6%) did not mention any reporting details. The MAH signature is an important component of a DHCP letter. We found that qualified persons responsible for pharmacovigilance ($n$ = 87; 51%) and medical directors ($n$ = 78; 46%) signed most of the letters. However, four letters (2.4%) were missing MAH signatures. Moreover, the number of pages per letter was assessed. Of 169, 112 letters (66%) presented the safety information within the two-page limit. Forty-seven letters (28%) had three pages, six letters (3.5%) had four pages, three letters (1.8%) had five pages, and only one letter (0.6%) reached six pages in length.

Finally, the letters were assessed based on the MAHs' names. Most of them were distributed by Roche ($n$ = 23), Novartis ($n$ = 17), or Janssen ($n$ = 15; see Table 5); respectively. Of 169 letters, 61 DHPC letters were compliant with the major assessment criteria adopted from the European pharmacovigilance guidelines (Tables 6 and 7).

## 4 | DISCUSSION

To the best of our knowledge, this study was the first of its type in the Middle East to investigate and describe DHPC letters. The practice of DHPC letters is suggested to be a good tool to support safe and effective use of medicinal products as a risk minimization measure.[6,7] Following the establishment of the pharmacovigilance program at the SFDA in 2009, the department has actively started to prepare infrastructure for pharmacovigilance activities related to individual case

**TABLE 4** Letters associated with immunosuppressant agents

| Trade name | Generic name | Number of letters |
|---|---|---|
| Gilenya | Fingolimod | 6 |
| Fegona | Fingolimod | 3 |
| Benlysta | Belimumab | 2 |
| Cellcept | Mycophenolate mofetil | 2 |
| Myora | Mycophenolate mofetil | 1 |
| Tysabri | Natalizumab | 1 |
| Imnovid/Pomalyst | Pomalidomide | 1 |
| Actemra | Tocilizumab | 2 |
| Xeljanz | Tofacitinib | 2 |
| Stelara | Ustekinumab | 1 |
| Arava | Leflunomide | 1 |
| Revlimid | Lenalidomide | 1 |
| Myfortic | Mycophenolate mofetil | 1 |
| Lemtrada | Alemtuzumab | 1 |
| Simulect | Basiliximab | 1 |
| Esbriet | Pirfenidone | 1 |
| Total | | 27 |

safety reports, periodic safety update reports, and risk management plans. Later and more gradually, the SFDA has begun to focus on risk communications as part of risk management planning.[1] Additionally, the SFDA adopted its GVP guideline from the European guideline; there are similarity in most of the DHPC letter requirements. The SFDA guidelines include a template for DHPCs that clarifies the elements that need to be included when preparing DHPC letters.[4,6] These include date; active substance; name of medicinal product and main message; MAH name; brief description of the safety concern; recommendations for risk minimization (e.g., contraindications, warnings, precautions of use); recall information if applicable, including pharmacy or patient level and date of recall; a statement indicating that the information is being sent in agreement with the national medicines authority; and further information on the safety concerns and recommendations. Also, the reason for disseminating the DHPC letter at this point in time, a reminder of the need to report adverse reactions in accordance with the national spontaneous reporting system and reporting procedures, details on how to access the national spontaneous reporting system, MAH contact point, and appendices that include a list of literature references if applicable.[4,5]

Within Saudi Arabia, the first DHPC letter was released in 2011. From 2011 to 2019, 169 DHPC letters were disseminated on the SFDA website. Theses limited number of letters released by pharmaceutical companies in Saudi Arabia could be due to several reasons include that, (1) the concept of pharmacovigilance is considered new for both pharmaceutical companies and regulatory authority in the Middle East in general and in Saudi Arabia in specific as it was actually started in 2009, moreover, (2) no enough interaction between both stakeholders. However, the annual number of DHPC letters was notably increased from 2011 to 2019 (Table 2). That trend could be related to increased awareness of the need for DHPC letters, a more rigorous evaluation processes by the SFDA, or to the emerging safety issues raised during that time. Upon evaluating the available letters on

**TABLE 5** DHPC letters classified by marketing authorization holders

| MAH | Number of letters (*N* = 169) |
|---|---|
| Roche | 23 |
| Novartis | 17 |
| GSK | 15 |
| Janssen | 15 |
| Pfizer | 11 |
| Bayer | 9 |
| Sanofi | 9 |
| Amgen | 8 |
| Servier | 6 |
| Saudi Pharmaceutical Industries & Medical Appliances Corporation | 4 |
| Boehringer | 4 |
| AstraZeneca | 3 |
| Hikma | 3 |
| Gilead | 3 |
| Saudi Arabian Japanese Pharmaceutical Company Limited (SAJA) | 3 |
| Merck Sharp & Dohme | 3 |
| Bristol Myers Squibb | 2 |
| Celgene | 2 |
| Astellas | 2 |
| Dallah Health | 2 |
| Jazeera Pharmaceutical Industries | 2 |
| Merck | 2 |
| Riyadh Pharma | 2 |
| Tabuk pharmaceuticals | 2 |
| Novo Nordisk | 2 |
| Cigala GP | 1 |
| Deef | 1 |
| Eipico | 1 |
| Lilly | 1 |
| Julphar | 1 |
| Jamjoom Pharma | 1 |
| Sandoz | 1 |
| Oman Pharmaceutical Products | 1 |
| Tamer GP | 1 |
| Biologi | 1 |
| Algorithm Sal | 1 |
| Arab Pharmaceutical Manufacturing's | 1 |
| Pierre Fabre | 1 |
| Remedica | 1 |
| Pfizer, Bayer, Bristol Myers Squibb, Boehringer, & SAJA (shared letter) | 1 |
| Cinfa | 1 |

**TABLE 6** Main assessment criteria adopted from European pharmacovigilance guidelines

a. 2-page limit
b. Logo provided
c. Date mentioned
d. Trade name mentioned
e. Summary
f. Reason for dissemination
g. Agreement with SFDA
h. Reporting statement for SFDA & MAH
i. MAH contact information
j. Signature

**TABLE 7** Letters per marketing authorization holder compliant with criteria mentioned in (Table 6)

| MAH compliance with European pharmacovigilance guideline requirements | Number of letters/ total | Percent compliance |
|---|---|---|
| Algorithm SAL | 1/1 | 100% |
| Remedica | 1/1 | 100% |
| Julphar | 1/1 | 100% |
| Lilly | 1/1 | 100% |
| Biologi | 1/1 | 100% |
| Boehringer | 3/4 | 75% |
| Saudi Pharmaceutical Industries & Medical Appliances Corporation | 3/4 | 75% |
| Merck Sharp & Dohme | 2/3 | 66.7% |
| Bristol Myers Squibb | 1/2 | 50% |
| Dallah Health | 1/2 | 50% |
| Riyadh Pharma | 1/2 | 50% |
| Novo Nordisk | 1/2 | 50% |
| Merck | 1/2 | 50% |
| Tabuk pharmaceuticals | 1/2 | 50% |
| Saudi Arabian Japanese Pharmaceutical Company Limited | 1/2 | 50% |
| Jazeera Pharmaceutical Industries | 1/2 | 50% |
| Novartis | 8/17 | 47% |
| Pfizer | 4/11 | 36.3% |
| Gilead | 1/ 3 | 33.3% |
| GlaxoSmithKline | 5/15 | 33.3% |
| Hikma | 1/3 | 33.3% |
| Bayer | 3/9 | 33.3% |
| Sanofi | 3/9 | 33% |
| Roche | 7/23 | 30% |
| Servier | 1/6 | 16.6% |
| Janssen | 2/15 | 13.3% |

the SFDA website, we found that most of the safety concerns were related to antineoplastic and immunosuppressant agents. This can be expected because of the nature of these medications, as they depress the immune system, and due to the nature of the diseases they treat.[11-13] Furthermore, this area of therapy is considered relatively new in the market, so the drug safety profiles for these types of medications are not well known. We also noted that the issue of restrictions on combining different classes of medications that act on RAAS was a huge consideration in a certain period. That was mainly related to the risk of hyperkalemia associated with combining RAAS inhibitors[13,14]. The letters disseminated at that time aimed to increase the safety of the treated patients. After the risk of hyperkalemia with RAAS combinations, recommendations to minimize cardiac risks, severe cutaneous reactions, and diabetic ketoacidosis were notable.

In compliance with the current guidelines, almost all letters mentioned the title and reason for dissemination. These are considered important sections to involve HCPs with the distributed letters. Moreover, the logo and the date of the letter were mentioned in all letters. That confirmed the commitment of the MAHs and the regulatory body to distributing the letters with good timing relative to the safety issues raised. Additionally, the MAH logo sends a good message to the recipients (HCPs) that the MAHs are concerned about their products and they show their responsibility to ensure patient safety. Details on reporting information to both SFDA and MAH were mentioned in all letters. The reporting reminders in the letters encourage HCPs to report adverse drug reactions to the right destination. Moreover, many letters were signed by qualified persons responsible for pharmacovigilance or by medical directors, which conceded good oversight practices. On the other hand, it is questionable that a high proportion of the letters did not mention agreement statements with the SFDA. This is considered crucial information—generally, the MAH cannot release a DHPC letter without authorization approval, to avoid sending any confusing messages. Moreover, many letters did not include MAH contact information, and many did not mention the trade names of the medicinal products of interest. We believe that mentioning the contact information helps HCPs reach MAHs easily in case they need further assistance.

To ensure patient safety and minimize the risk of adverse events, DHPC letters must be communicated efficiently to HCPs. The pharmacovigilance guidelines recommend that the letter should summarize, highlight, and present the safety information as appropriate and not exceed 2 pages to maximize letters' readability and to achieve the intended purpose.[2,5] According to those criteria, a good number of letters that presented the safety information within the two-page limit were found. This is important to ensure that they will be read by the HCPs amid busy schedules, maximizing the benefit of the letters. Having some letters over 2 pages in length could limit their benefit. Therefore, it is important for authorities to stress this point whenever possible.

Most distributed DHPCs were by Roche ($n$ = 23), Novartis ($n$ = 17), and Janssen ($n$ = 15; see Table 5); respectively. These were mainly related to the types of medications that these MAH manufacture and market. For example, Roche's and Novartis' letters dealt mainly with safety concerns related to biological compounds (immunosuppressants and antineoplastics). On the other hand, Janssen disseminated letters related mainly to their glucose-lowering agents and other products, including opioids, antiepileptics, and antipsychotics.

The letters were classified by MAH, and their compliance with the requirements of interest were evaluated. These requirements include a 2-page limit, logo, date of the letter, trade name, safety concern summary, reason for dissemination, agreement with SFDA, reporting statement for SFDA and MAH, MAH contact information, and signatures. Of 169 letters, only 61 DHPC letters complied with the requirements (Tables 6 and 7). When several MAHs produce the same active substance that needs a DHPC letter to be issued, a single consistent message should be delivered. Sending a single letter will reduce the cost to MAHs and achieve the letter's goal, as HCPs will receive only one message regarding different brands, saving their time and maximizing the benefit of the information (e.g., see Table 5). Whenever possible and appropriate, it is advised that HCP organizations or learned societies be involved during the preparation of DHPC letters to ensure that the information they deliver is useful to the target audience.[4]

This study has an advantage as it is the first study evaluating the DHPC in Saudi Arabia as per our best of knowledge. However, our study has limitation that It is depending on the letters that are available in the SFDA website, and there is a chance that there are some letters have been approved by SFDA and not posted on its website during the study period.

## 5 | CONCLUSION

Our results suggest that the DHPC letters disseminated by MAHs in Saudi Arabia have an acceptable level of compliance with national guidelines. However, some important information was missing from number of letters. To enhance the awareness of assessing the letters by any regulatory authority, we recommend having a specific department within the authority to deals with the risk communication letters. Moreover, using a checklist containing the DHPC elements based on the approved guidelines in letters evaluation is highly suggested. In addition, trained the team to evaluate the letters to maintain their excellent work is recommended. Indeed, any regulatory authority should carefully assess such letters based on its approved guidelines.

## 6 | DATA SHARING STATEMENT

The data of this study will be available upon acceptance and after request.

### DISCLOSURE

The authors declare that there is no conflict of interest regarding the publication of this article.

### AUTHOR CONTRIBUTIONS

Dr. Thamir Alshammari designed the study and the data collection form. Dr. Hajer M. Al-saleh conducted the study by extracted the obtained data and filled the collection form. Dr. Alshammari analyzed the data and Dr. Al-saleh prepared and wrote the manuscript. Both Dr. Alshammari and Dr. Alsaleh review the final form of the manuscript. The authors made the decision to submit this manuscript for publication, and vouch for the accuracy and completeness of the data and analyses.

### OPEN RESEARCH BADGE

This article has earned Open Data, Open Materials and Preregistered Research Design badges. Data, materials and the preregistered design and analysis plan are available in the article.

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