Medicines Adverse Reactions Committee

Meeting date	11/09/2025	Agenda item	3.2.3
Title	**Calcium channel blockers and drug reaction with eosinophilia and systemic symptoms (DRESS)**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name, strength, formulation**		**Sponsor**
amlodipine	Vasorex 2.5 mg, 5 mg, 10 mg tablets		REX Medical
diltiazem	Cardizem CD 180 mg, 240 mg capsules		Pharmacy Retailing
	Diltiazem CD 120 mg capsules		Clinect
felodipine	Felo ER 5 mg, 10 mg tablets		Viatris
	Plendil ER 2.5 mg, 5 mg, 10 mg tablets		Clinect
nifedipine	Nyefax Retard 20 mg tablets		Douglas
nimodipine	Nimotop 30 mg tablets		Bayer
	Nimotop 0.2 mg/mL solution for infusion		Bayer
verapamil	Isoptin 40 mg, 80 mg tablets		Viatris
	Isoptin SR 120 mg, 240 mg tablets		Viatris
	Isoptin 5 mg/2mL solution for injection		Viatris
Pharmac funding	All funded on the community schedule except for nimodipine		
Previous MARC meetings	Not previously discussed. DRESS with macrolide antibiotics was discussed at the 159th meeting on 11 Sep 2014		
Prescriber Update	DRESS syndrome – Monitor for long-term sequelae (Sep 2020) Re-ad-DRESS-ing the risk of DRESS with cautious titration (Sep 2022)		
Classification	Prescription medicine		
Usage data	In 2024 approximately 407,071 people received an initial dispensing of a Pharmac-funded calcium channel blocker from a community pharmacy		
Advice sought	**The Committee is asked to advise:** • On the strength of the evidence for an association between DRESS and calcium channel blockers. The Committee could consider this for each individual calcium channel blocker, or for the medicines as a group. • If any regulatory action is required.		

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1 PURPOSE

In August 2024, Medsafe received a report of a 67-year-old patient who experienced drug reaction with eosinophilia and systemic symptoms (DRESS) following treatment with atorvastatin, diltiazem and amlodipine. None of the data sheets for these three medicines list DRESS but all three are included in a literature article by Stirton et al (2022). Although atorvastatin was reported as a suspect medicine, [redacted] it could be excluded as a suspect. This is the only New Zealand report retrieved where DRESS is coded with a calcium channel blocker as the suspect medicine.

The purpose of this paper is to review information on DRESS with calcium channel blockers to confirm if any regulatory action is needed.

2 BACKGROUND

2.1 Calcium channel blockers

For the purposes of this review, calcium channel blockers are defined as those included in the ATC group of 'C08 Calcium Channel Blockers' as determined by the WHO. The ATC index is publicly available: https://atcddd.fhi.no/atc_ddd_index/

The calcium channel blockers included in this review (as shown on the cover page) are those with a Medsafe registration of 'consent given' under the C08 Calcium channel blockers ATC group.

2.1.1 Mechanism of action

Calcium channel blockers prevent the influx of calcium ions through L (long)-type channels into vascular smooth muscle, myocardium and cardiac conducting system (sino-atrial and atrioventricular node) cells [1]. Based on clinical activity they form two distinct groups [1]:

- Dihydropyridines (amlodipine, felodipine, isradipine, nifedipine, nicardipine, nimodipine) act selectively on vascular smooth muscle to cause vasodilation. They have little effect on myocardial cells.
- Non-dihydropyridines (diltiazem, verapamil) are less selective and act to reduce cardiac conduction and heart rate as well as acting on vascular smooth muscle. Verapamil has a greater effect on conduction and contractility and minimal effect on smooth muscle, while diltiazem acts on arterial smooth muscle.

According to the medicine data sheets, calcium channel blockers are generally used to treat hypertension and angina. Verapamil is also used to treat arrhythmias. Nimodipine is different in that it is used to prevent and treat ischaemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorrhage of aneurysmal origin.

2.1.2 Usage

The number of people who have received an initial dispensing of a calcium channel blocker by year is shown in Table 1 and Figure 1. Based on this data:

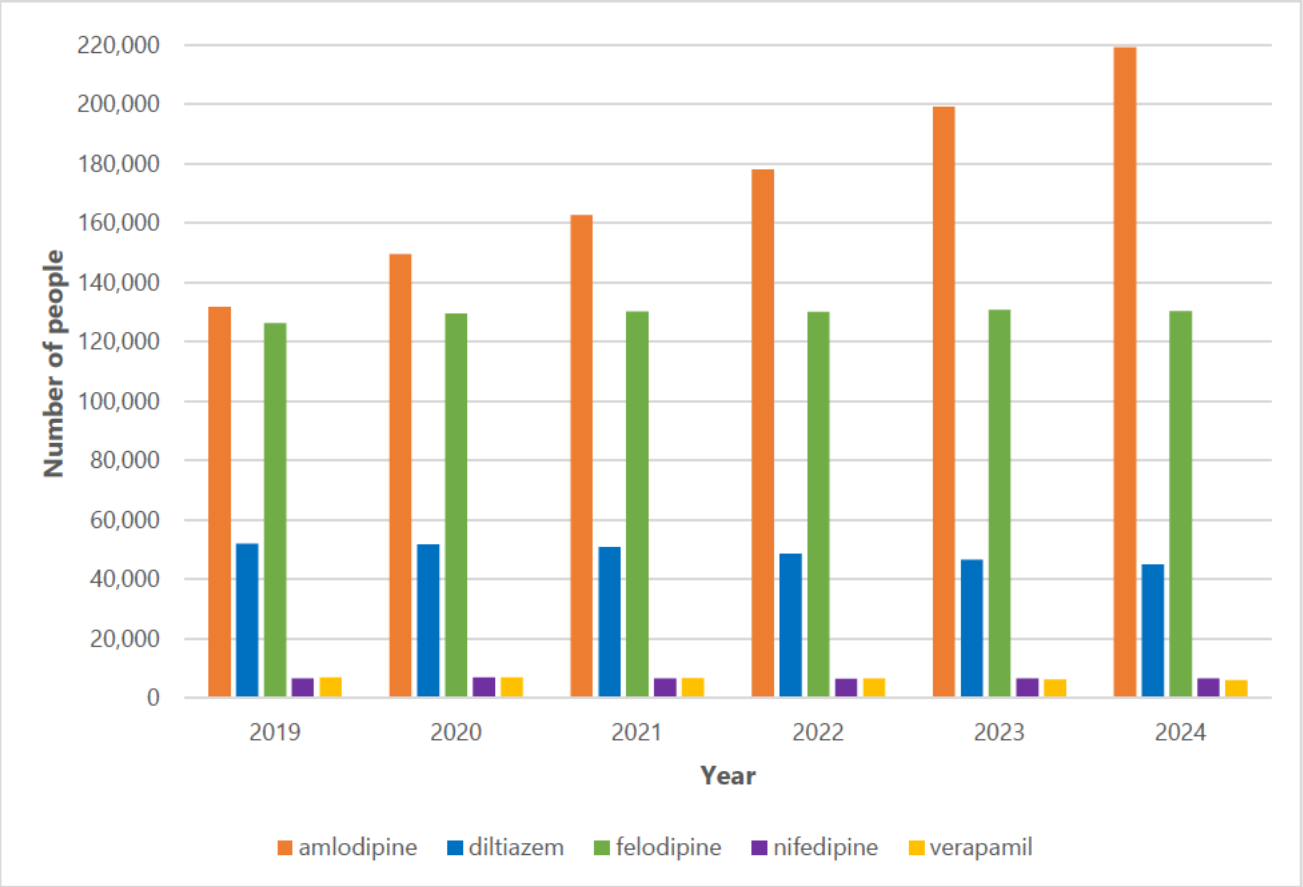
- amlodipine and felodipine are the most widely used medicines in this group
- the use of amlodipine is increasing over time
- the use of diltiazem is slowly decreasing over time.

Table 1: Number of people with an initial dispensing of a calcium channel blocker, by year

	2019	2020	2021	2022	2023	2024
amlodipine	131,561	149,547	162,672	178,073	199,285	219,227
diltiazem	51,921	51,690	50,905	48,561	46,511	44,977
felodipine	126,323	129,524	130,169	130,079	130,695	130,347
nifedipine	6,480	6,793	6,540	6,394	6,539	6,546
nimodipine	not funded					
verapamil	6,875	6,785	6,580	6,490	6,216	5,974
Total	323,160	344,339	356,866	369,597	389,246	407,071

Source: Pharmaceutical Data web tool (2019 data extracted 13 Jan 2025, 2020-2025 data extracted 16 Oct 2025)

Figure 1: Number of people with an initial dispensing of a calcium channel blocker, by year



Source: Pharmaceutical Data web tool (2019 data extracted 13 Jan 2025, 2020-2025 data extracted 16 Oct 2025)

2.2 Drug reaction with eosinophilia and systemic symptoms (DRESS) [2]

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, idiosyncratic, T-cell mediated hypersensitivity reaction characterised by varied combinations of skin eruption, fever, facial swelling, lymphadenopathy, haematological abnormalities, and visceral involvement.

Compared to other severe cutaneous adverse drug reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP), DRESS has a more heterogenous clinical presentation making diagnosis more challenging.

The triad of drug-induced fever, rash and eosinophilia has been recognised since the 1930s. It was originally recognised as an anticonvulsant hypersensitivity syndrome and other terms have been proposed over time. In 1996, the term DRESS was proposed to encompass these similar reactions and differentiate them from other severe drug reactions without eosinophilia. The lowercase e (DReSS) is sometimes used to denote that eosinophilia is not always present and other haematological abnormalities may be seen.

The term drug-induced hypersensitivity syndrome (DiHS) was suggested by Japanese investigators to describe a version of DRESS requiring the presence of viral reactivation. Although still somewhat controversial, the terms DRESS and DiHS are often used interchangeably to describe the same syndrome.

2.2.1 Epidemiology

DRESS is estimated to occur in 0.9 to 2 per 100,000 patients per year [3]. In hospitalised patients, DRESS accounts for 10 to 20% of all cutaneous adverse reactions. DRESS occurs predominantly in adults though it may occur in children [3]. The mean age of onset is between 40 and 60 years [2].

2.2.2 Aetiology and risk factors

A clear medicine trigger can be identified in the majority of DRESS cases (approximately 80%). In the remaining 10-20% of cases, the strength of medicine causality is less clear, and in 2% of cases no medicine exposure is present [3].

A large proportion of cases (about 75%) are due to the following high-risk medicines [3]:

- aromatic antiepileptics (eg, carbamazepine, phenytoin, lamotrigine)
- allopurinol
- sulfonamides (eg, sulfasalazine, dapsone, co-trimoxazole)
- antituberculosis agents (eg, rifampicin, ethambutol, isoniazid, pyrazinamide)
- mexiletine
- minocycline
- vancomycin.

Lower-risk medicines include beta-lactams (eg, amoxicillin, ampicillin, piperacillin), NSAIDs (eg, celecoxib, ibuprofen, diclofenac), olanzapine, fluoxetine, imatinib, sorafenib, vemurafenib, omeprazole, and raltegravir [3].

The most common comorbidities of DRESS include epilepsy, HIV, hypertension, diabetes and hyperuricaemia, likely related to the culprit medicine rather than an intrinsic predisposition to DRESS [2].

2.2.3 Pathogenesis

DRESS is classified as a delayed type IVb, and sometimes IVc, hypersensitivity reaction [2]. Although the exact pathogenesis is not fully understood, two main pathogenetic mechanisms are thought to be involved: a drug-specific immune response, and a human herpesvirus (HHV) reactivation with a subsequent antiviral immune response [3].

- Drug-specific immune response: The role of drug-specific immune response in the pathogenesis of DRESS has been proven based on positive patch tests to some causative medicines as well as the in vitro demonstration of drug-specific CD4+ and CD8+ T cells that produce large amounts of TNF-alpha and IFN-gamma.

- Herpesviridae reactivation: Reactivation of viruses from the Herpesviridae family (eg, HHV-6, HHV-7, Epstein-Barr virus, cytomegalovirus) is a known phenomenon associated with DRESS and occurs in up to 75% of patients.

However, the mechanisms and timing of viral reactivation in relation to the drug-specific immune response have not been clarified and the role of virus reactivation in the pathogenesis of DRESS remains controversial. One hypothesis is that viral reactivation occurs as a result of an immunodeficiency state. An alternative hypothesis is that certain medicines (eg, valproate, amoxicillin) may directly increase HHV-6 and CMV replication [3].

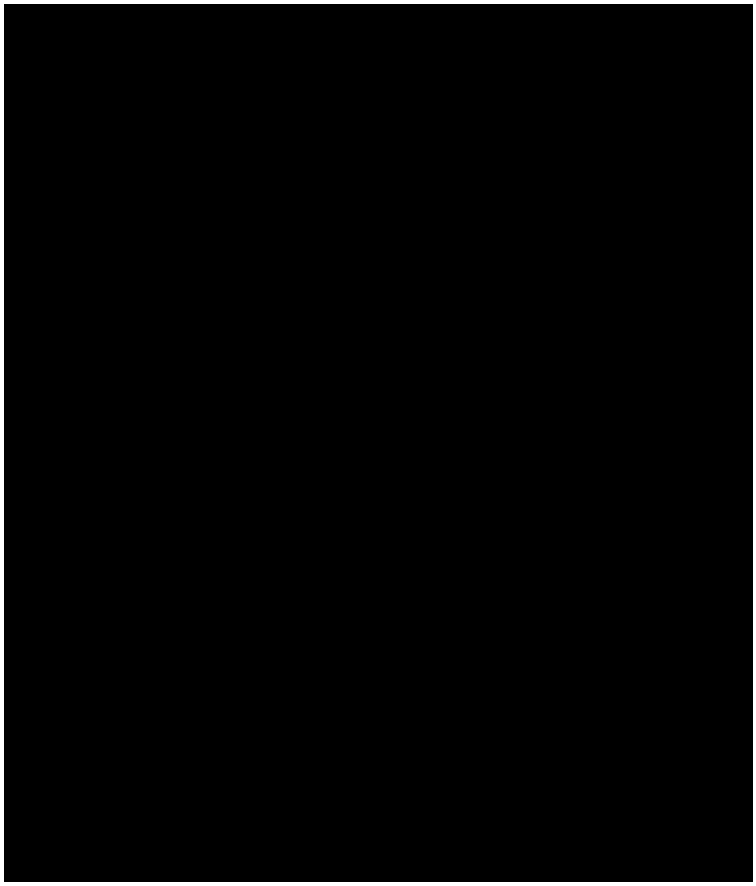
2.2.4 Immune changes

DRESS is characterised by a variety of haematological abnormalities including leukocytosis, atypical lymphocytosis and eosinophilia. A heterogenous profile of cytokines and chemokines has also been found. While eosinophilia is not universally present, a Th2-type (T helper type 2) response can be seen with eosinophil-associated cytokines such as IL-4, IL-5 and IL-13 [2].

2.2.5 Genetic predisposition

HLA alleles are one of the most important risk factors in the development of DRESS. Therefore, ethnic background is an important predisposing factor. Mechanistically, it is thought the suspect medicine interacts with a particular HLA to form a complex-hapten which is then presented to naïve T cells via the T cell receptor to stimulate an immune response. Currently known medicine-HLA associations with DRESS are shown in Table 2.

Table 2: DRESS-associated HLA alleles according to medicine and ethnicity



Source: Table 2 of Stirton et al (2022) [2]

Comments:

Edinur et al (2012) [4] described HLA polymorphism in Polynesian (n=36) and Māori (n=114) individuals.

The most common HLA genes observed in Polynesians are HLA-A*02, -A*24, -B*56, -C*01, -DQB1*03 and -DRB1*04. When comparing HLA data between Polynesians and Māori, the predominant HLA class I alleles observed in Polynesians such as HLA-A*02, -A*24, -B40, -B55 and -C*01 are also common in Māori with full ancestry (MFA) except for HLA-B*56 which is slightly reduced in MFA.

The only one of these HLA genes mentioned in Table 1 is -A*24, which is relevant for DRESS with phenytoin and lamotrigine.

2.2.6 Clinical presentation

Most commonly, DRESS begins with a **flu-like prodrome** of malaise, pharyngitis, fever and lymphadenopathy. The progression of signs and symptoms can be slow and varied, but many studies report fever in most patients (between 75-100%). Fever typically precedes the cutaneous eruption by several days [2].

Compared to other SCARs, the time to onset **(TTO) is more delayed, typically between 2-8 weeks**. On re-exposure to the suspect medicine, symptoms can develop in hours to days. TTO also depends on the medicine. For example, antiepileptics and allopurinol tend to have longer latency periods compared to antibiotics or radiocontrast media, which have been shown to have lag times less than 14 days from exposure [2].

The **cutaneous manifestations** of DRESS are diverse. Typically, more than 50% of total body surface area is involved. The most common morphologies are monomorphic maculopapular/morbilliform, urticated papular, and exfoliative erythroderma. Distribution is typically symmetric often starting on the face, upper trunk and upper extremities then spreading to the lower extremities. Cutaneous manifestations are polymorphic in around 85% of cases which can include secondary features such as pustules, purpura, vesicles, bullae and cheilitis. Facial oedema is also characteristic of DRESS (reported in up to 76% of cases) and may be a distinguishing feature from more mild forms of DRESS or maculopapular eruption [2].

There are a range of **haematological abnormalities** seen in DRESS. Hypereosinophilia is the most common finding, present in 52-92% of patients across multiple studies. Eosinophil counts are often dramatically increased. Leukocytosis with early neutrophilia and delayed monocytosis is the next most common abnormality, followed by atypical lymphocytosis [2].

Liver injury is the most common **visceral manifestation** in DRESS, seen in 53-90% of cases [3]. Elevated liver enzymes (cholestatic, mixed and hepatocellular) is the most common finding [2]. Acute liver failure is rare and may require liver transplantation [3].

The next most involved organ is the kidney. Renal involvement ranges from mild AKI to severe interstitial nephritis, sometimes resulting in permanent end-stage renal disease. Elderly patients, allopurinol-associated DRESS, and those with pre-existing kidney disease are at highest risk of renal impairment [2].

2.2.7 Diagnosis

Making a diagnosis of DRESS can be challenging due to its delayed-onset, stepwise presentation and variable clinical features [2]. The RegiSCAR score (Table 3) is frequently used particularly in North America and Europe, and it is also used in New Zealand [2, 5]. A limitation is the inability to allow for an early diagnosis of DRESS [2].

There is no clear consensus on the ideal method of determining the causative medicine [2]. Two key considerations are [3]:

- Exposure to high-risk medicines
- Prolonged latency: The time to onset is typically 2-8 weeks after medicine exposure. Medicines taken for less than 2 weeks or more than 3 months before the onset of DRESS are unlikely to be the culprit. In some cases, medicines that have been stopped prior to the onset of disease can still be suspected if the medicine or metabolite is still present in the body due to a long half-life or impaired clearance.

Causality may be further supported by positive patch tests and/or in vitro tests (eg, lymphocyte proliferation assay) [3].

Table 3: RegiSCAR validation scores for DRESS

Source: Table 4 of Stirton et al (2022) [2]

2.2.8 Treatment

The mainstay of treatment remains systemic steroids alongside identification and immediate withdrawal of the culprit medicine. Supportive care with close monitoring, fluid and electrolyte replacement, haemodynamic support and adequate skin care is also imperative [2].

2.2.9 Prognosis

The mortality rate in DRESS is frequently quoted at 10%. More recent studies have found lower estimates ranging from 1.7% to 8.8%. Mortality in the paediatric population is reported to be 5.4%. The most common causes of death are hepatic failure, multiorgan failure and sepsis. Poor prognostic factors for DRESS include pancytopenia, older age, CMV reactivation, allopurinol or minocycline-induced DRESS, and renal and hepatic involvement [2].

Signs and symptoms of DRESS may persist for weeks after withdrawal of the suspect medicine with a mean recovery time around 6-9 weeks. Furthermore, there have been multiple reports of patients developing autoimmune sequelae after DRESS including Hashimoto's thyroiditis, Grave's disease, fulminant type 1 diabetes, systemic lupus erythematosus, alopecia areata, vitiligo, autoimmune haemolytic anaemia, thrombotic thrombocytopenic purpura and rheumatoid arthritis. Other non-immune long-term sequelae include end-stage renal disease requiring haemodialysis. Multiple drug hypersensitivity syndrome (MDH), defined as an immune mediated hypersensitivity reaction to two or more unrelated medicines confirmed by skin or by in vitro testing, is a recently recognised entity that may occur after DRESS [2].

2.3 Data sheets

2.3.1 New Zealand

DRESS isn't mentioned in any of the calcium channel blocker NZ data sheets. However, other skin reactions are mentioned (Table 4).

Table 4: Skin reactions mentioned in calcium channel blocker data sheets

Product	Section 4.4 warning	Section 4.8 undesirable effects
amlodipine Vasorex		Skin: alopecia, discolouration of the skin, increase in sweating, purpura and urticaria Allergic reactions: angioedema, erythema multiforme, pruritus, rash
diltiazem Cardizem Diltiazem	erythema multiforme and/or exfoliative dermatitis infrequently reported	Skin: erythema, petechiae, photosensitivity, pruritus, urticaria, lichenoid drug eruption
felodipine Felo Plendil		Skin: rash, pruritus, urticaria, photosensitivity reactions, leukocytoclastic vasculitis
nifedipine Nyefax		Skin: erythema Immune system: pruritus, urticaria, rash
nimodipine Nimotop		Immune system: rash
verapamil Isoptin		Skin: hyperhidrosis, angioedema, Stevens-Johnson syndrome, erythema multiforme, alopecia, itching, pruritus, purpura, rash maculopapular, urticaria

Source: Medicine data sheets (accessed 12 Nov 2025)

2.3.2 International

A search for the same calcium channel blocker data sheets in Australia, UK, Ireland and US also found that DRESS isn't listed. Some of the UK and US data sheets describe other SCARs which are not described in the corresponding NZ or Australian data sheets.

3 SCIENTIFIC INFORMATION

3.1 Published literature

This section includes case reports where a calcium channel blocker was used concomitantly with another medicine suspected to have caused DRESS or when a calcium channel blocker was a co-suspect medicine.

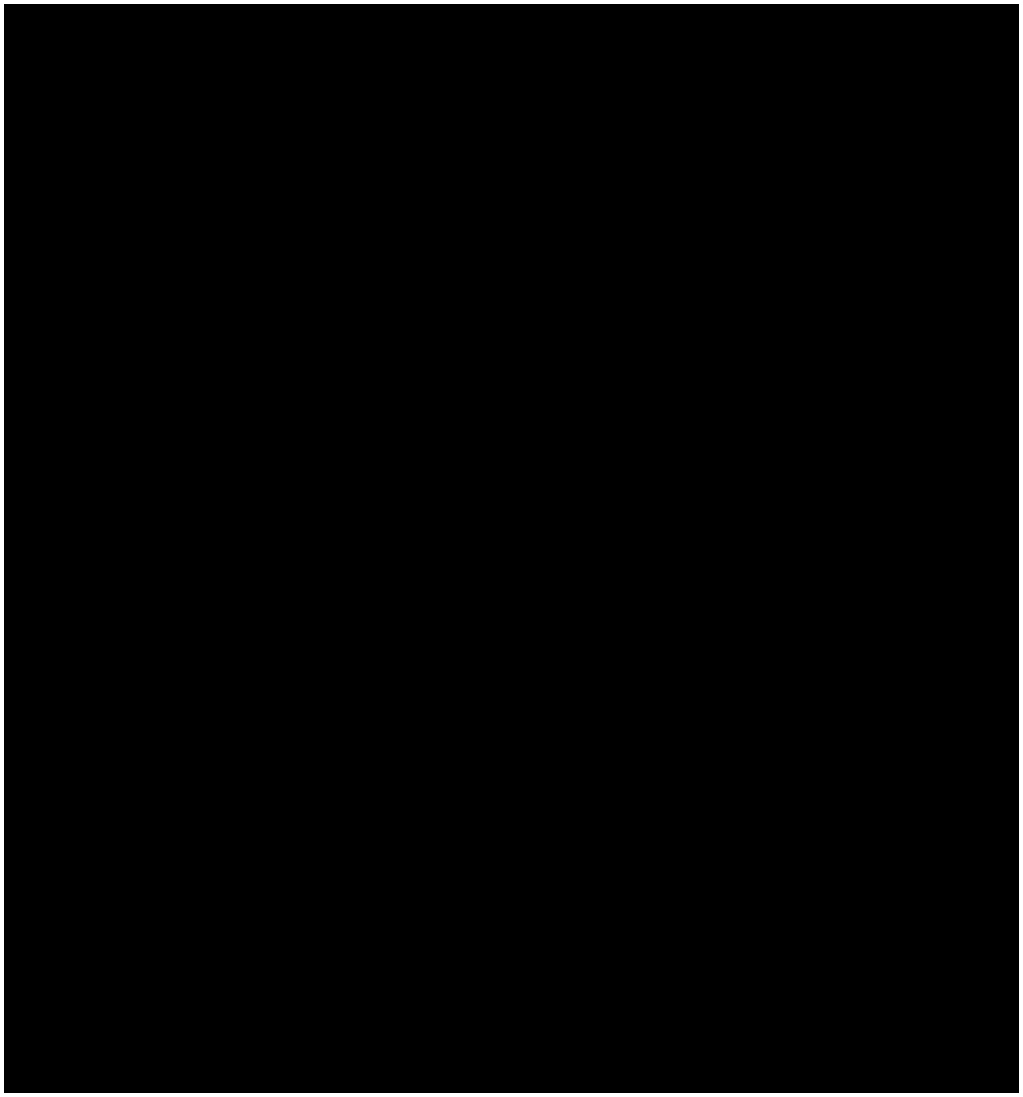
3.1.1 Stirton et al 2022 – Review of DRESS/DIHS [2]

Title: Drug reaction with eosinophilia and systemic symptoms (DReSS)/Drug-induced hypersensitivity syndrome (DiHS) – Readdressing the DReSS

The authors present a comprehensive review on the most recent research and literature on DReSS with emphasis on pathogenesis, clinical features, diagnosis, confirmatory testing modalities, and treatment.

The most common DReSS-inducing medicines are anticonvulsants, allopurinol, sulfonamides and antibiotics. A comprehensive list of medicines associated with DReSS is shown in Table 5.

Table 5: Medicines associated with DReSS



Comments:

The three suspect medicines (amlodipine, diltiazem, atorvastatin) in the case that prompted this review are all included in the table. Amlodipine (dihydropyridine) and diltiazem (non-dihydropyridine) are the only calcium channel blockers in the table.

This article wasn't found by any of the PubMed searches performed. However, it can be found through a Google search.

3.1.2 Ang et al 2010 – Retrospective analysis of drug-induced hypersensitivity syndrome [6]

Title: Retrospective analysis of drug-induced hypersensitivity syndrome: A study of 27 patients.

This was a retrospective case series of patients with a diagnosis of drug-induced hypersensitivity syndrome (DIHS) treated in a hospital in Singapore from Jan 2003 to Jan 2008.

A total of 27 patients were analysed. The 3 most consistent features were:

1. History of drug exposure (100%)
2. A morbilliform cutaneous eruption in 81.5% of patients
3. Systemic involvement with hepatitis (96.3%), haematologic abnormalities (81.5%), and fever (77.8%).

Superficial perivascular dermatitis was the most common skin biopsy specimen finding with tissue eosinophilia occurring in half the biopsy specimens. Severe complications included renal failure requiring dialysis in 2 patients and hyperthyroidism and myocarditis occurring in one patient.

The most common culprit medicines in the study included anticonvulsants (4 patients on carbamazepine, 5 patients on phenytoin), antibiotics (4 patients on Maloprim (pyrimethamine and dapsone), 4 patients on co-trimoxazole, 1 patient on both ciprofloxacin and metronidazole), 6 patients on allopurinol, NSAIDs (2 patients on indomethacin, 2 patients on diclofenac) and 6 patients on other medicines.

Of the 6 patients on other medicines, there was an 83-year-old female on tolterodine, nifedipine and atenolol. After 14 days, she experienced a morbilliform rash with facial oedema, fever, hepatitis, and eosinophilia during hospitalisation. There was no mucosal involvement and no renal impairment.

Comments:

This case series describes 27 cases of DIHS of which one patient was on tolterodine (no approved products in NZ), nifedipine and atenolol (not listed in the NZ data sheet). The authors note 9 cases had more than one culprit medicine and identifying the main culprit is often difficult due to polypharmacy.

3.1.3 Chan et al 2018 – Cefalexin, perindopril/amlodipine case report [7]

Title: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: Case report of severe multiorgan involvement to perindopril/amlodipine combination antihypertensive.

A 77-year-old Hungarian patient presented with a generalised morbilliform eruption. The pruritic eruption initially started on his chest then extended to the limbs over 2 days. The patient had completed a course of cephalexin 3 weeks prior and had pruritus without rash 1 week after finishing the cephalexin which was diagnosed as a mould allergy by his immunologist.

The only abnormal lab result on admission was mild eosinophilia which normalised the next day. Histology findings from the skin biopsy were suggestive of a drug reaction. By then, the patient's only medicine was perindopril 5 mg in combination with amlodipine 5 mg. These medicines were stopped, and prednisone was started and produced cutaneous improvement. The discharge diagnosis was drug reaction secondary to either cephalexin or perindopril/amlodipine.

Three months after discharge, the patient restarted perindopril/amlodipine and had an erythematous skin eruption 3 days later. This time, there was associated fever, lethargy, neck swelling and peripheral oedema. He also reported a 5 kg unintentional weight loss over 4 weeks. On examination, he was erythrodermic, tachycardic and febrile. There was an exfoliative facial dermatitis and diffuse maculopapular eruption over the

arms, trunk and lower limbs. Also noted were facial and acral swelling and prominent non-tender left cervical lymphadenopathy.

Laboratory results showed anaemia, leukocytosis, isolated eosinophilia, high C-reactive protein, and hepatic dysfunction. There was also acute renal impairment. A CT scan found a suspicious right lung nodule and multisite lymphadenopathy. The 2 skin biopsies found moderate spongiosis and superficial dermal infiltrate of lymphocytes with eosinophils. Lymph node and bone marrow biopsy showed eosinophilic infiltrates without malignant cells. Renal biopsy found numerous eosinophils with florid tubulointerstitial nephritis, which is consistent with renal involvement in DRESS syndrome.

DRESS syndrome secondary to amlodipine/perindopril was diagnosed by applying the RegiSCAR scoring system. To the authors' knowledge, there are no reports of amlodipine or perindopril individually or in combination being implicated with DRESS.

Comments:

The patient was taking a combination product containing both amlodipine and perindopril and it is difficult to know the role each component played in the development of DRESS. Cephalexin could also be considered a co-suspect medicine in this case.

3.1.4 Helmandollar et al 2018 – Amlodipine & meloxicam case report [8]

Title: Diffuse vesiculobullous eruption with systemic findings

A 61-year-old female patient developed fever and generalised vesiculobullous including oral and vaginal mucosa. Symptoms of fever, sore throat and fatigue were also reported. Her medical history was pertinent for hypertension with recent addition of amlodipine approximately 6 weeks prior. She was also recently restarted on meloxicam which she had used intermittently in the past for osteoarthritis-related joint pain.

Initial laboratory tests demonstrated elevated liver function tests, leucocytosis and eosinophilia. Histopathologic examination of the punch biopsy revealed a bulla with sub-epidermal split and numerous neutrophils. Direct immunofluorescence demonstrated broad deposition of IgA along the dermal-epidermal junction. These findings were consistent with an overlap between drug induced linear IgA bullous dermatosis (LABD) and DRESS.

The authors note drug induced LABD and DRESS are independently both rare conditions, and it is even more uncommon to see the two concurrently in the same patient. It was thought the patient's presentation was drug-induced with either amlodipine or meloxicam being the most likely cause. Both medicines were discontinued and the patient started on a prolonged prednisone taper. She was also started on dapsone given the diagnosis of LABD. Following discharge from hospital, the skin progressively cleared with residual hyperpigmentation. At 3-month follow-up laboratory values had normalised.

The patient has intermittently used meloxicam since then without any known sequela. Rechallenge with amlodipine has not been done.

Comments:

The authors suspect amlodipine and meloxicam as the most likely cause of drug induced LABD and DRESS in this patient. Symptoms appeared 6 weeks after starting amlodipine, which fits within the usual time to onset of DRESS (2-8 weeks). Meloxicam had been used intermittently before and after LABD and DRESS making it a less likely cause.

3.1.5 Tolcyzk et al 2024 – Amlodipine concomitant case report [9]

Title: Diagnostic challenges in an adolescent hospitalized with fever and rash

A 15-year-old male with no significant past medical history presented to ED with a 12-day history of fever and rash. He had acne and was started on minocycline 2 weeks prior to the onset of symptoms. Physical examination revealed diffuse erythroderma and an evolving maculopapular rash involving his trunk,

extremities, palms and soles. Initial lab workup revealed leucocytosis, abnormal lymphocytes and marked eosinophilia. He was started on empiric vancomycin and clindamycin due to concern for toxic shock syndrome.

Dermatology was consulted due to concern for minocycline-induced DRESS. Skin biopsy revealed eosinophils consistent with drug eruption. Biopsy results coupled with lab findings of eosinophilia, abnormal lymphocytes and transaminitis supported DRESS as the leading differential diagnosis. He was started on IV methylprednisolone with initial improvement of rash and resolution of fevers. His condition then deteriorated. Paediatric nephrology was consulted for blood pressure control and initiated isradipine and later amlodipine.

His final diagnosis was relapsing minocycline-induced DRESS with multisystem organ involvement. While he had evidence of hepatic involvement at initial presentation, subsequent relapsing episodes included renal involvement and worsening hepatic function. The diagnosis was further supported by marked initial response to steroid treatment and findings of drug-induced tubulointerstitial nephritis on renal biopsy and drug-induced liver injury on liver biopsy.

Comments:
Amlodipine is an unlikely cause of DRESS in this patient because it was started for blood pressure control after the onset of DRESS symptoms.

3.1.6 Ben Fadhel et al 2020 – Nifedipine concomitant case report [10]

Title: DRESS syndrome following furosemide administration: An unusual association

A 67-year-old man was admitted to the nephrology department for hypertension, gout and chronic renal failure. He received a multidrug therapy including captopril, nifedipine, allopurinol and furosemide. Six weeks after starting this treatment, he developed a maculopapular itchy and oedematous skin reaction, facial oedema and fever.

Laboratory findings showed 2200/mm^3 of eosinophils (20%). Creatinine clearance decreased from 18.9 to 14.4 mL/min. Lactate dehydrogenase was at 600 IU/L (normal range 190-390 IU/L). Chest X-ray showed an interstitial lung injury. Skin biopsy findings were in accordance with a hypersensitive reaction.

The symptoms were thought to result from a hypersensitive reaction and allopurinol was withdrawn. A few days later, the skin eruption extended and eosinophilia increased to 2600/mm^3. Because the patient was dehydrated, furosemide was withdrawn and symptoms resolved completely three weeks later. Furosemide was then suspected to have induced DRESS syndrome and allopurinol was reintroduced without any incident.

A patch test with furosemide performed six weeks later was negative. The patient was given bumetanide, another sulfonamide loop diuretic with recurrence of symptoms 2 months later. Bumetanide was withdrawn with a complete resolution of both clinical and biological symptoms within 3 weeks.

The REGISCAR scoring system was used with a score of 6 which made the diagnosis of DRESS syndrome definite. The authors state DRESS syndrome appeared to be related to furosemide in view of a clear temporal relationship between medicine intake and onset of symptoms (6 weeks) and the resolution of the reaction some weeks after medicine withdrawal. The recurrence of DRESS syndrome after bumetanide suggests a possible cross reactivity between furosemide and bumetanide due to their chemical similarity.

Comments:
The authors didn't include much information on captopril and nifedipine which the patient was also taking alongside allopurinol and furosemide. It is assumed treatment with captopril and nifedipine continued.

3.1.7 Palafox-Olvera et al 2025 – Nifedipine concomitant case report [11]

Title: Drug hypersensitivity: When systemic symptoms and pustules converge.

Overlap severe cutaneous adverse drug reactions (SCARs) are defined as cases that fulfil diagnostic criteria for at least two of these drug-associated reactions, according to scoring systems. The authors present a case of an overlapping SCAR.

A 53-year-old female was treated with metformin and linagliptin for diabetes, and nifedipine for high blood pressure. Secondary to an isolated seizure, she was treated with phenytoin and 5 weeks later she presented with erythema in the chest region accompanied by pruritus that spread to the abdomen.

Treatment with antihistamines was initiated with poor improvement progressing to generalised erythema and fever. On admission, she presented with generalised polymorphic skin lesions of a maculopapular rash and bullous lesions on the forearms, as well as pustular lesions on the face.

Laboratory findings included leukocytosis with neutrophilia (67%), eosinophilia (3,880/mm^3) and acute kidney injury. Biopsy showed chronic interface dermatitis, superficial perivasculitis and eosinophilia. According to the RegiSCAR scoring system with 4 points and the EuroSCAR score with 6 points, both considered the case as probable. The patient began steroid therapy with methylprednisolone followed by reduced doses of prednisone.

The authors conclude the patient presented with a severe cutaneous adverse reaction 5 weeks after starting phenytoin which showed overlap according to the scales. Secondary ambiguities among SCARs, confirmed cases of overlap are rare. In the acute stage of the disease, early identification of SCARs can be difficult due to overlapping features.

Comments:

This article was published in Spanish and the English translation is only available for the abstract. This is a case of overlapping SCAR. It is unknown which SCARs were overlapping but the keywords for the article included ‘DRESS’ and ‘Acute exanthematous pustulosis’. The suspect medicine in this case appears to be phenytoin, with concomitant nifedipine, metformin and linagliptin.

3.2 Spontaneous case reports

3.2.1 New Zealand

The case report (158266) that triggered this review describes a 67-year-old female [redacted] patient who experienced DRESS following treatment with atorvastatin, diltiazem and amlodipine (Table 6). [redacted] The patient also developed LFT derangement. [redacted]

Table 6: Medicine details for case 158266

[redacted]					

Comments:

As described earlier in this memo, there is no clear consensus on determining the suspect medicines causing DRESS. However, it seems that in this case, atorvastatin could be excluded as a suspect [redacted] Verapamil is the only calcium channel blocker indicated for atrial fibrillation. [redacted]

Using Qlik, there are a total of 209 cases coded to the PT Drug reaction with eosinophilia and systemic symptoms. There are no cases reporting nifedipine, nimodipine or verapamil as medicines (concomitant or suspect). There are 10 cases reporting amlodipine, diltiazem and/or felodipine as medicines (concomitant or suspect) which are summarised in Table 7:

- Median age was 55.5 years (range 37 to 68 years).
- [redacted]
- Only the index case reported a calcium channel blocker as a suspect medicine, the remainder are concomitant medicines.
- Suspect medicines: allopurinol (n=4), antibiotic (n=4), index case reporting 2 calcium channel blockers and a statin.
- [redacted]
- [redacted]
- [redacted]

Table 7: Summary of cases reporting a calcium channel blocker in association with DRESS (n=10)

ID	Date	Age	M/F	Ethnicity	Medicine(s)	Reaction(s) PT	Notes
097968	Oct 2011	60	M	[redacted]	vancomycin*, warfarin, cefuroxime, ferrous sulphate, erythropoietin, felodipine, insulin, calcitriol, calcium, ezetimibe + simvastatin, furosemide, lisinopril, ondansetron, Oxynorm, metoclopramide, fentanyl	Drug reaction with eosinophilia and systemic symptoms	[redacted]
104043	Sep 2012	68	F	[redacted]	allopurinol*, colchicine, atorvastatin, cilazapril, felodipine, metoprolol, doxazosin	Drug reaction with eosinophilia and systemic symptoms	[redacted]
105058	Dec 2012	52	F	[redacted]	allopurinol*, insulin glargine, metoprolol, simvastatin, felodipine, aspirin, doxazosin, epoetin, calcitriol, furosemide, quinapril, lactulose	Drug reaction with eosinophilia and systemic symptoms	[redacted]
105251	Jan 2013	46	M	[redacted]	allopurinol*, digoxin, felodipine, dabigatran atorvastatin, Champix (varenicline)	Drug reaction with eosinophilia and systemic symptoms	[redacted]
114011	Oct 2014	68	M	[redacted]	normal immunoglobulin*, amlodipine, chlortalidone, omeprazole, metformin, lisinopril, insulin	Drug reaction with eosinophilia and systemic symptoms	[redacted]
118049	Sep 2015	55	M	[redacted]	cotrimoxazole*, amlodipine, candesartan, loratadine	Drug reaction with eosinophilia and systemic symptoms	[redacted]
124432	May 2017	37	M	[redacted]	allopurinol*, diclofenac, amlodipine, colchicine, atenolol	Drug reaction with eosinophilia and systemic symptoms	[redacted]

137826	Jul 2020	54	F	[redacted]	vancomycin*, diltiazem, aspirin, furosemide, spironolactone, warfarin, omeprazole	Drug reaction with eosinophilia and systemic symptoms, optic neuritis	[redacted]
147968	Jun 2023	56	M	[redacted]	co-amoxiclav*, metoprolol, heparin, levetiracetam, amlodipine, budesonide nasal, paracetamol, Molaxole, Laxsol	Drug reaction with eosinophilia and systemic symptoms, eosinophilia, rash	[redacted]
158266 (**source of signal**)	Aug 2024	67	F	[redacted]	atorvastatin*, diltiazem*, amlodipine*, dexamethasone	Drug reaction with eosinophilia and systemic symptoms, liver function test abnormal, drug eruption	[redacted]

Source: New Zealand Pharmacovigilance Database (data extracted via Qlik suspected adverse reactions to medicines app on 10 Nov 2025, data current to 7 Sep 2025). ADRSearch Access database used to retrieve case details. PDFs downloaded via Access and EXT-Medwatch for full case details where available.

Notes:

- * = suspect medicine, M = male, F = female
- Calcium channel blocker shown in green text, statin in orange text
- The case that triggered this review is highlighted in green

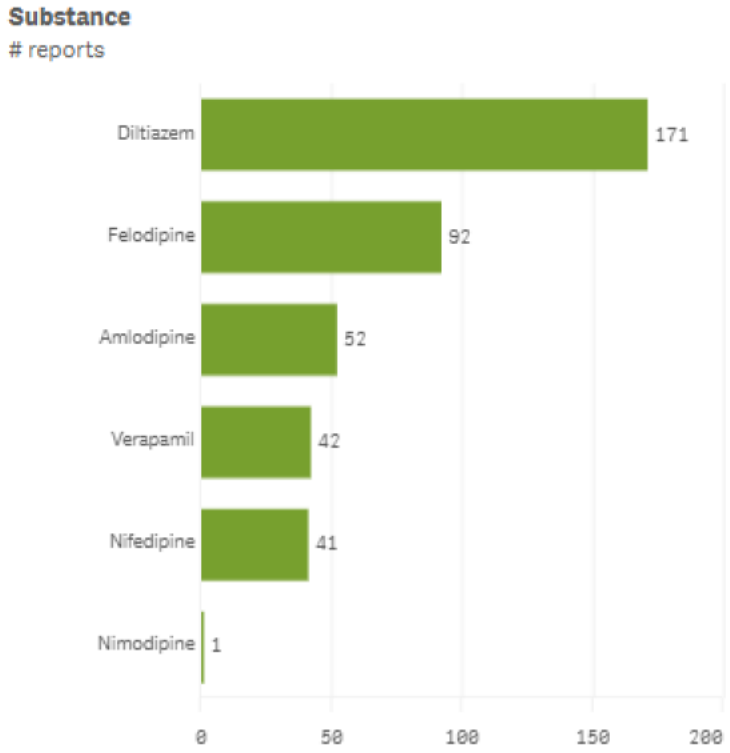
Comments:

There could be an undercounting of cases due to coding practices.

Drug-induced hypersensitivity syndrome (DIHS) is sometimes used interchangeably with DRESS. The hierarchical MedDRA (our dictionary for reaction terms) structure maps DIHS back to DRESS so DIHS cases would also be returned from the search.

Using the standardised MedDRA query (SMQ) Drug reaction with eosinophilia and systemic symptoms, there is a total of 61,858 cases in the pharmacovigilance database. Of these, 398 cases report a calcium channel blocker as a suspect medicine (Figure 2). Note that this SMQ includes unspecific PTs such as rash (n=111). Manual review is needed to ascertain if there are cases with more than one co-reported term that would be more suggestive of DRESS.

Figure 2: Calcium channel blockers with SMQ DRESS (N=398)



Source: New Zealand Pharmacovigilance Database (data extracted via Qlik suspected adverse reactions to medicines app on 10 Nov 2025, data current to 7 Sep 2025).

Comments:

SMQs are groupings of MedDRA terms that relate to a defined medical condition or area of interest. They aid in the identification and retrieval of potentially relevant reports. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data etc.

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

DRESS is a SCAR characterised by a varied presentation involving a rash, fever, facial swelling, lymphadenopathy, haematological abnormalities and visceral involvement. Compared to other SCARs, it has a longer time to onset, and its heterogenous clinical presentation can make it hard to diagnose.

The most common medicines associated with DRESS are antiepileptics, allopurinol, sulfonamides and antibiotics. There have been a number of *Prescriber Update* articles on DRESS with the most recent one in September 2022.

The receipt of a CARM case reporting DRESS in a patient treated with atorvastatin, diltiazem and amlodipine prompted this review on whether calcium channel blockers are associated with DRESS. This is the only local case with a calcium channel blocker as the suspect medicine. A further 9 cases report a calcium channel blocker as a concomitant medicine. [redacted].

Information in the published literature of DRESS with calcium channel blockers are lacking. A review article by Stirton et al (2022) listed amlodipine and diltiazem as medicines associated with DRESS. There are 2 case reports in the literature where amlodipine was considered a co-suspect medicine. A further 3 case reports in the literature describe amlodipine or nifedipine as a concomitant medicine.

None of the calcium channel blocker data sheets here or internationally include information on DRESS. However, skin reactions are described in all data sheets and some also include other SCARs (eg, SJS, AGEP).

5 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the evidence for an association between DRESS and calcium channel blockers. The Committee could consider this for each individual calcium channel blocker, or for the medicines as a group.
- If any regulatory action is required.

6 ANNEXES

1. Stirton et al 2022

7 REFERENCES

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