

CLINICAL PRACTICE GUIDELINE

Selinexor Supportive Care Guidelines

Authored by X-PERIENCE Steering Committee,
endorsed by Myeloma Scientific Advisory Group

MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG) TO MYELOMA AUSTRALIA (MA)
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Introduction

As of September 2022, the combination of XPOVIO® (selinexor) and dexamethasone +/- bortezomib for the treatment of relapsed and/or refractory multiple myeloma (RRMM) were made available on the Australian Pharmaceutical Benefits Scheme.¹ This decision was based on the positive outcomes from the BOSTON and STORM studies.^{3,5}

Selinexor with its unique mechanism of action and as a first-in-class agent means that there is limited clinical experience of its use among haematologists in Australia. Consequently, the **X-PERIENCE Steering Committee**, comprising of 12 Australian expert physicians in the specialty of multiple myeloma, have come together to help fill this gap. These recommendations have been endorsed by the Medical and Scientific Advisory Committee of Myeloma Australia and produced as guidelines. While the ongoing learning process of acquainting ourselves to newly approved drugs is a familiar process, it can be challenging to build our experience as individual physicians. Hence, this recommendations document has been developed to help build on our collective local clinical experience and share our knowledge, while aspiring to develop Australian best practice in the management of relapsed refractory multiple myeloma.

The Product Information for XPOVIO®² is the gold standard guidance when prescribing and administering this agent. In addition to this, our goal is to provide practical strategies that aim to maximise the efficacy of XPOVIO® and to address the predictable toxicities. Following several Steering Committee meetings, consensus was reached for the following recommendations.

Registered indications²

XPOVIO® is indicated:

→ In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior line of therapy.

→ In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory medicinal product (IMiD), and an anti-CD38 monoclonal antibody (mAb).

Pivotal trials leading to TGA registration of XPOVIO®

BOSTON study^{3,4}

The efficacy of XVd (XPOVIO®, bortezomib and dexamethasone) was evaluated in BOSTON, a global, randomised, open label, active-controlled Phase 3 study of patients with multiple myeloma who had received 1-3 prior treatment regimens. Compared with Vd (bortezomib and dexamethasone), once-weekly XVd was associated with significant improvements in median progression-free survival (PFS) of 13.93 months versus 9.46 months and overall response rate (ORR) of 76.4% versus 62.3%.

These results become more striking when one considers that XVd-treated patients received 40% less bortezomib and 25% less dexamethasone, with 37% fewer clinic visits, than Vd-treated patients during the first 24 weeks of the study. Additionally, XVd conferred improvements in median PFS and ORR relative to Vd in patient subgroups defined by cytogenetic risk status except t(14;16) and baseline disease characteristics, including increased number of prior lines of therapy, prior treatment with lenalidomide, reduced creatinine clearance and patients aged ≥65 years of age.¹

The most frequent grade 3-4 adverse events were thrombocytopenia, anaemia and fatigue. The rate of greater than grade 2 neuropathy were less frequent in the XVd arm.

Table One

Safety Profile

Most Common TEAEs (In ≥10% in either group), n (%)	XVd arm (n=195)		Vd arm (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematological Adverse Events				
Thrombocytopenia	117 (60)	77 (39)	55 (27)	35 (17)
Anemia	71 (36)	31 (16)	47 (23)	20 (10)
Neutropenia	29 (15)	18 (9)	12 (6)	7 (3)

Table One

Safety Profile

Most Common TEAEs (In ≥10% in either group), n (%)	XVd arm (n=195)		Vd arm (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-Hematological Adverse Events				
Fatigue	82 (42)	26 (13)	37 (18)	2 (1)
Nausea	98 (50)	15 (8)	20 (10)	0
Diarrhea	63 (32)	12 (6)	51 (25)	1 (<1)
Peripheral neuropathy†	63 (32)	9 (5)	96 (47)	18 (9)
Decreased appetite	69 (35)	7 (4)	11 (5)	0
Weight loss	51 (26)	4 (2)	25 (12)	4 (2)
Asthenia	48 (25)	16 (8)	27 (13)	9 (4)
Constipation	33 (17)	0	35 (17)	3 (1)
Cough	35 (18)	15 (8)	30 (15)	0
Insomnia	31 (16)	12 (6)	32 (16)	4 (2)
Back pain	30 (15)	9 (5)	29 (14)	2 (1)
Pneumonia‡	35 (18)	24 (12)	34 (17)	21 (10)
Pyrexia	30 (15)	3 (2)	22 (11)	2 (1)
Cataract	42 (22)	17 (9)	13 (6)	3 (1)
Vomiting	40 (21)	8 (4)	9 (4)	0
Peripheral edema	23 (12)	1 (1)	26 (13)	0
Dyspnea	18 (9)	1 (1)	27 (13)	5 (2)
Bronchitis	24 (12)	3 (2)	20 (10)	1 (<1)
URTI	35 (18)	5 (3)	30 (15)	1 (<1)

TEAE: Treatment-emergent adverse events, URTI: Upper respiratory tract infection Vd: Bortezomib and dexamethasone, XVd: Selinexor, bortezomib, and dexamethasone

* Three patients from this group who did not receive any doses of study drug were excluded from the safety population.

† Includes four grade 5 events: three (2%) cases of pneumonia and one (1%) case of bronchitis.

‡ Includes four grade 5 events: three (1%) cases of pneumonia and one (<1%) case of anemia.

§ Includes high-level MedDRA term "peripheral neuropathies NEC."

¶ Includes pneumonia, lung infection, hemophilus infection, pulmonary sepsis, and pneumonia respiratory syncytial viral, pneumonia pneumococcal, pneumonia influenza viral, pneumonia parainfluenza viral, pneumonia bacterial, and pneumonia fungal infections.

Grosicki S, et al. Lancet. 2020;396(10262):1568–73

STORM study⁵

STORM was a phase 2b, multicentre, open-label study involving patients with RRMM who received Xd (XPOVIO® and dexamethasone). The median number of previous regimens was 7. A partial response or better was observed in 26% of patients and a minimal response or better was observed in 39% of patients. In patients who had a partial response or better or a minimal response or better, the median overall survival was 15.6 months.

Starting a patient on XPOVIO®

XPOVIO® in combination with bortezomib and dexamethasone (XVd).²

Recommended starting dose and schedule:

TREATMENT	RRMM in combination with bortezomib and dexamethasone (XVd) 35-day cycle XPOVIO® days 1, 8, 15, 22, 29 Bortezomib days 1, 8, 15, 22 Dexamethasone 20mg day of and day after bortezomib		
	XPOVIO®	Bortezomib	Dexamethasone
DOSE	40-80 mg PO	1.3 mg/m ² SC	20 mg PO
SCHEDULE	Once weekly (Day 1)	Once weekly (Day 1) for 4 weeks, then 1 week off	Twice weekly (Day 1 and 2 each week)

The median delivered dose of XPOVIO® in the Boston study was 80 mg weekly².

XPOVIO® in combination with dexamethasone (Xd).⁵

Recommended starting dose and schedule:

TREATMENT	RRMM in combination with dexamethasone (Xd)	
	XPOVIO®	Dexamethasone
DOSE	40-80 mg PO	20 mg PO
SCHEDULE	Once weekly (Day 1)	Twice weekly (Day 1 and 2 each week)

The median delivered dose of XPOVIO® in the STORM study was 113.6 mg/week (approx. 60 mg twice weekly)²

While the starting doses of selinexor on the Boston and STORM study ranged from 100mg weekly to 80mg twice weekly, a weekly starting dose of selinexor should be considered for patients. In frail patients, consider starting with a lower dose and up-titrate doses as tolerated.

Adverse Events: The most common adverse events are nausea and vomiting, weight loss and anorexia, hyponatremia, thrombocytopenia , neutropenia and fatigue / asthenia.

Patient monitoring early in treatment

As most adverse events occur in the first one to two months,⁹ the following recommendations are suggested by the Steering Committee early in treatment:

→ **Monitor patients weekly during first four weeks**

- Assess for tolerability within the first week
- Maintain a low threshold for dose reduction as early as week two
- Check weight

Consider weekly bloods including:

- Full blood count
- Urea and electrolytes
- Complete metabolic profile

→ **Low platelets and/or low sodium can be predictors of adverse effects**

→ **Review monthly face-to-face**

- Dose interruptions and dose reductions in the BOSTON study occurred most often during first and second cycles¹⁰
- Reviewing the patient symptom diary for at least the first cycle is crucial.
- Adverse events are largely dose and schedule dependent⁹

Setting expectations with patient

Managing patient expectations regarding potential side effects and how to manage them will help support patients to maintain treatment through this crucial time, optimising the clinical benefit of XPOVIO®.

There are three key principles:

1. Dose modification to balance efficacy with safety/tolerability
2. Proactive management of AEs with proactive supportive care
3. Ongoing monitoring: for XPOVIO®, adverse events are generally self-limiting, reversible, and manageable with dose modifications and supportive care.

BOX ONE

Recommendations for consequently adverse events

Selinexor has a short mean half-life of 6–8 hours² and consequently adverse events can be managed efficiently.

- Set expectations with patient for possible dose delays and/or reductions to allay any confusion or anxiety.
- Inform patient that even the lower doses are therapeutic.
- Ask patient to keep a daily record of the symptoms for at least the first cycle, so that adverse reactions can be proactively addressed.

Prophylactic antiemetic regimen

Nausea and vomiting:

The most common non-haematologic adverse event with XPOVIO® is nausea and vomiting.^{2,9,10,12,132}

Before starting therapy with XPOVIO®, commence treatment with **two** prophylactic antiemetics.

Double anti-nausea coverage

Administer prophylactic 5-HT₃ antagonist and/or other anti-nausea agents, prior to and during treatment with XPOVIO®¹

→ Ondansetron 8 mg PO (or other 5-HT₃ antagonist of choice) 30 to 60 minutes prior to each dose and continued for every 8 hours for a few days following dosing.^{6,7}

→ **AND** additional agents, eviQ Prevention of Anti-cancer therapy Induced Nausea and Vomiting (AINV) Guidelines recommend olanzapine at clinician's discretion for the prevention of nausea and vomiting⁸ / Olanzapine 2.5 mg - 5.0 mg PO nocte^{6,7,9}

→ Antiemetics may be tapered after 8 weeks of therapy as required

Add third antiemetic as needed^{6,7}

Once weekly oral dose of:

Akynzeo® (netupitant 300 mg + palonosetron 0.5 mg) (PBS-reimbursed)

If Akynzeo® is used, ondansetron should only be added for breakthrough nausea 72 hours after Akynzeo® is taken.

OR

Aprepitant *

*not currently PBS reimbursed for this indication

→ **Administer intravenous fluids to prevent dehydration if required and replace electrolytes as clinically indicated**

Adverse reaction	Actions
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration, or malnutrition) OR Grade 1 or 2 vomiting (≤ 5 episodes per day)	<ul style="list-style-type: none"> → Antiemetics may be tapered after 8 weeks of therapy as required → Initiate additional anti-nausea medications to supplement the required 5-HT3 antagonists, per institutional guidelines, eviQ or NCCN → Add olanzapine nocte for 1-2 months if appropriate
Grade 3 nausea (inadequate oral caloric or fluid intake) OR Grade ≥ 3 vomiting (≥ 6 episodes per day)	<ul style="list-style-type: none"> → Interrupt XPOVIO® and provide supportive care → Monitor until nausea or vomiting has resolved to Grade ≤ 2 or baseline → Initiate additional anti-nausea medications → Restart XPOVIO® at 1 dose level lower

Comment from Steering Committee: Consider maintaining XPOVIO® dose for 1 week for Grade 1 or 2 vomiting.

→ Nausea/vomiting was highest within first cycle of treatment and dropped substantially for each subsequent cycle¹⁴

→ Incidence of nausea (all grades) was 72% with Xd and 50% with XVd with the use of antiemetic prophylaxis²

Weight loss and anorexia^{2, 9,10,12,13}

Provide nutritional support and appetite stimulants as clinically required

Adverse reaction	Actions
Grade 2 weight loss (10% to <20%) OR Grade \geq 3 anorexia associated with significant weight loss or malnutrition	→ Interrupt XPOVIO® and provide supportive care → Rule out other causes → Consider a repeat nutritional consultation and nutritional supplements → Commence supportive care per institutional guidelines, eviQ and NCCN → Monitor until weight returns to more than 90% of baseline weight → Restart XPOVIO® at 1 dose level lower

Example of supportive care medications:

→ Mirtazapine or olanzapine 2.5–5.0 mg orally in the evening^{9,12}

Hyponatraemia^{2, 9,10,12}

→ Correct sodium levels for:

→ Concurrent hyperglycaemia (serum glucose >150 mg/dL)

→ High serum paraprotein levels

→ Assess hydration status and manage hyponatraemia per clinical guidelines (intravenous saline and/or salt tablets as appropriate), including dietary review.

Adverse reaction	Actions
Sodium level \leq 130 mmol/L	<ul style="list-style-type: none"> → Interrupt XPOVIO® and provide supportive care → Monitor until sodium levels return to $>$ 130 mmol/L → Restart XPOVIO® at 1 dose level lower

Additional example of supportive care:

→ Salty snacks

Thrombocytopenia^{2,9,10,12}

Thrombocytopenia is the most common hematologic adverse event with XPOVIO® and is often exacerbated by lower starting platelet counts in heavily pretreated patients.¹¹

→ Administer platelet transfusion and/or other treatments as clinically indicated per Institutional Guidelines.

Adverse reaction	Actions
Platelet Count 25,000 to $<$ 75,000/ μ L	→ Reduce XPOVIO® by 1 dose level
Reduce XPOVIO® by 1 dose level	<ul style="list-style-type: none"> → Interrupt XPOVIO® and provide supportive care → Restart XPOVIO® at 1 dose lower after bleeding has resolved
Platelet Count $<$ 25,000/ μ L	<ul style="list-style-type: none"> → Interrupt XPOVIO® and consider supportive care → Monitor – until platelet count returns to at least 50,000/μL → Restart XPOVIO® at 1 dose level lower

Comment from Steering Committee: Many patients will start off with platelet count $<75,000/\mu\text{L}$ due to disease. Consider reducing XPOVIO® dose if thrombocytopenia was due to XPOVIO®.

Neutropenia^{2,9,10,12}

→ Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF) per Institutional Guidelines.

Adverse reaction	Actions
Absolute neutrophil count of 0.5 to $< 1.0 \times 10^9/\text{L}$ without fever	→ Reduce XPOVIO® by 1 dose level
Absolute neutrophil count $< 0.5 \times 10^9/\text{L}$ OR febrile neutropenia	→ Interrupt XPOVIO® and provide supportive care → Monitor until neutrophil counts return to $1.0 \times 10^9/\text{L}$ or higher → Restart XPOVIO® at 1 dose level lower

Comment from Steering Committee: Consider using G-CSF first and reducing by 1 dose level if neutropenia persists despite GCSF support.

G-CSF agents:

- Filgrastim: 5 mcg/kg SC
- Pegfilgrastim: 6 mg SC

Fatigue^{2,12-14}

→ Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF) per Institutional Guidelines.

Adverse reaction	Actions
Grade 1 fatigue relieved by rest	<ul style="list-style-type: none">→ Reduce XPOVIO® by 1 dose level→ Initiate supportive care per institutional guidelines, eviQ and NCCN
Grade 2 fatigue lasting > 7 days OR Grade 3 fatigue not relieved by rest, limiting self-care ADL	<ul style="list-style-type: none">→ Interrupt XPOVIO® dose until resolved to Grade 1 or baseline.→ Initiate supportive care per institutional guidelines, eviQ and NCCN.→ Monitor for anaemia→ Restart XPOVIO® at 1 dose level lower

ADL: activities of daily living

The supportive care recommendations provided in this document are prepared by the X-PERIENCE Steering Committee in conjunction with Antengene and updated by the MSAG. This should not be relied upon as being complete or mandate any particular course of medical care. All treatment decisions are solely at the discretion of the treating physician or healthcare professional.

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