Ixazomib (Ninlaro®)

This Horizons Infosheet contains information on ixazomib (also known as Ninlaro®), a drug being investigated for the treatment of myeloma.

The Horizons Infosheet series provides information relating to novel drugs and treatment strategies that are currently being investigated for the treatment of myeloma. The series also aims to highlight the considerable amount of research currently taking place in the field of myeloma.

The drugs and treatment strategies described in the Horizons Infosheets may not be licensed and/or approved for use in myeloma. You may, however, be able to access them as part of a clinical trial.

What is ixazomib?

Ixazomib is a new drug being investigated for the treatment of myeloma.

Like bortezomib (Velcade®) and carfilzomib (Kyprolis®), ixazomib

belongs to a group of drugs known as proteasome inhibitors.

Unlike bortezomib and carfilzomib which are given subcutaneously (under the skin) and intravenously (into the vein), ixazomib is the first oral (by mouth) proteasome inhibitor to be developed – this means it can be taken at home as a tablet instead of being administered in the hospital.

What are proteasomes?

Proteasomes are large molecules which are present in all cells in the body. They are involved in the removal, breakdown and recycling of damaged proteins or those that are no longer needed by the cell.

How does ixazomib work?

Ixazomib works by binding to proteasomes and temporarily blocking their function, which stops them from breaking down unwanted proteins (Figure 1). This causes proteins to build up and become toxic, killing the cell.

Myeloma cells multiply more quickly than normal healthy cells and rely more heavily on proteasomes as they produce unwanted proteins at a faster rate. They are therefore much more sensitive to ixazomib.

Myeloma cells appear to be even more dependent on the actions of proteasomes than other types of cancer cells. This may be due to the need of the myeloma cells to dispose of the abnormal protein (paraprotein) they produce.

By blocking the function of the proteasome, ixazomib prevents the myeloma cells from growing and multiplying.

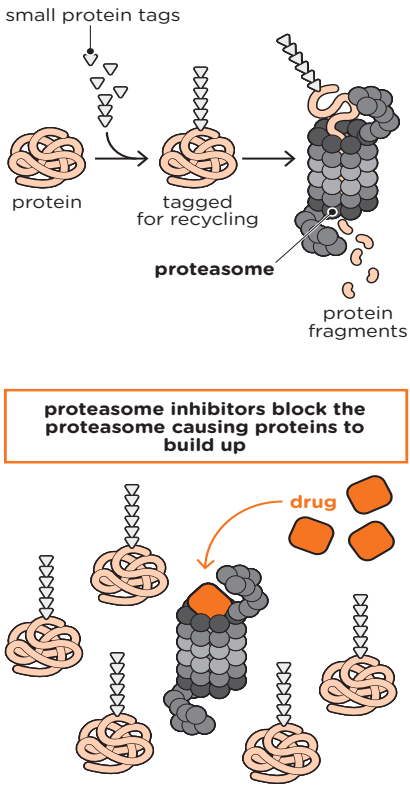

Figure 1. Mechanism of action of proteasome inhibitors.

How is ixazomib given?

Ixazomib can be given as a monotherapy (used on its own and not in combination with other drugs) but it has been shown to be most effective when used in combination with other myeloma treatments such as lenalidomide (Revlimid®) and dexamethasone.

The optimal dosage for ixazomib is 4mg taken on days 1, 8 and 15 of a 28 day treatment cycle. However, if you are unable to tolerate the side-effects of this dosage or if you have liver or kidney damage, it can be lowered to 3mg or 2.3mg accordingly.

When given in combination with ixazomib, lenalidomide is taken orally on days 1 to 21 and low-dose dexamethasone is taken orally on days 1, 8, 15 and 22 of each cycle.

The treatment is continuous until disease progression.

What evidence exists to support the use of ixazomib?

Results from clinical trials to date have shown that ixazomib can produce effective responses in both relapsed and newly diagnosed patients.

Data from the Phase III TOURMALINE MM-1 clinical trial showed that relapsed and/or refractory myeloma patients receiving ixazomib in combination with lenalidomide and dexamethasone had nearly 6 months longer progression free survival (the length of time following treatment before the myeloma starts to come back) compared to patients who received lenalidomide and dexamethasone alone.

Phase I/II clinical trials looking at the same combination in newly diagnosed patients showed a high overall response rate - 80% in patients treated with weekly ixazomib and 92% in patients given twice-weekly ixazomib. Median progression free survival in this group of patients was found to be over two years in patients treated both once- and twice-weekly.

What are the possible known side-effects of ixazomib?

The most common side-effects of ixazomib include: nausea, vomiting, constipation, diarrhoea, oedema (the retention of abnormally large amounts of fluid in the body, causing swelling), skin rash and back pain.

Like bortezomib, ixazomib can

also cause peripheral neuropathy (damage to the nerves that make up the peripheral nervous system causing pain, tingling and altered sensation). However, in clinical trials ixazomib has been shown to cause lower rates of peripheral neuropathy than bortezomib, possibly due to it being more targeted.

Ixazomib is known to cause low platelet counts, which may increase your risk of nose bleeds and bruising.

Is ixazomib currently available in any UK clinical trials?

For an up-to-date list of UK clinical trials involving ixazomib, visit the **Myeloma Trial Finder** on **www.myeloma.org.uk**

To be enrolled on a clinical trial, patients have to meet certain conditions known as eligibility criteria. You should speak to your doctor in the first instance if you are interested in taking part in a trial.

Availability of ixazomib in the UK

Before a drug can be widely used, it must first be licensed as a safe and effective treatment. This is usually done by regulatory authorities at a European level and involves a review of evidence from large scale clinical trials.

Normally, the licensed drug must then be approved by a UK drug appraisal body before it can be routinely prescribed by NHS doctors. The drug appraisal process differs from licensing - it compares how effective the newly-licensed drug is to existing drugs already in use on the NHS and decides whether it offers the NHS good value for money. The main body responsible for carrying out drug appraisals in England and Wales is the National Institute for Health and Care Excellence (NICE). NICE recommendations are usually adopted in Northern Ireland. Scotland's drug appraisal body is the Scottish Medicines Consortium (SMC).

For more information see the Health Technology Assessment (HTA) Infosheet from Myeloma UK

Ixazomib has been approved by the European Medicines Agency (EMA) for use in combination with lenalidomide and dexamethasone for relapsed myeloma patients who have received at least one previous treatment.

In December 2017, NICE

approved ixazomib in combination with lenalidomide and dexamethasone for English and Welsh patients who have received two or three prior treatments, through a government fund called the Cancer Drugs Fund (CDF). Under the CDF, NICE can issue a conditional 'yes' to promising drugs about which there is still some uncertainty regarding clinical effectiveness. Under this agreement, there is a two year period where more data on the effectiveness of the drug is collected. NICE then make a final decision as to whether it should be approved for routine use.

In Northern Ireland the Department of Health, Social Services and Public Safety usually reviews NICE guidance within three months of publication. However, there is currently a lack of clarity about the process for providing access in Northern Ireland to drugs approved via the CDF. Now that this approval has been granted via the CDF, Myeloma UK will be working with the DHSPSS to clarify their intentions in relation to funding ixazomib for patients in Northern Ireland.

The SMC has no current plans to appraise ixazomib.

Future directions

Ixazomib continues to be studied in different myeloma patient groups and in different treatment combinations. These trials will provide information about the safest and most effective way to use ixazomib in myeloma.

About this Horizons Infosheet

The information in this Horizons Infosheet is not meant to replace the advice of your medical team. They are the people to ask if you have questions about your individual situation. All Myeloma UK publications are extensively reviewed by patients and healthcare professionals prior to publication.

Myeloma UK wishes to thank Takeda Pharmaceuticals for reviewing this document for factual accuracy.

For a list of references used to develop our resources, visit **www.myeloma.org.uk/references**

To provide feedback on this publication, email **myelomauk@myeloma.org.uk**

Other information available from Myeloma UK

Myeloma UK has a range of publications available covering all areas of myeloma, its treatment and management.

To order your free copies or to talk to one of our Myeloma Information Specialists about any aspect of myeloma, call our Myeloma UK Infoline on **0800 980 3332** or **1800 937 773** from Ireland.

The Infoline is open from Monday to Friday, 9am to 5pm and is free to phone from anywhere in the UK and Ireland.

Information and support about myeloma is also available around the clock at **www.myeloma.org.uk**

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