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 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 drug development.

The drugs 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 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.

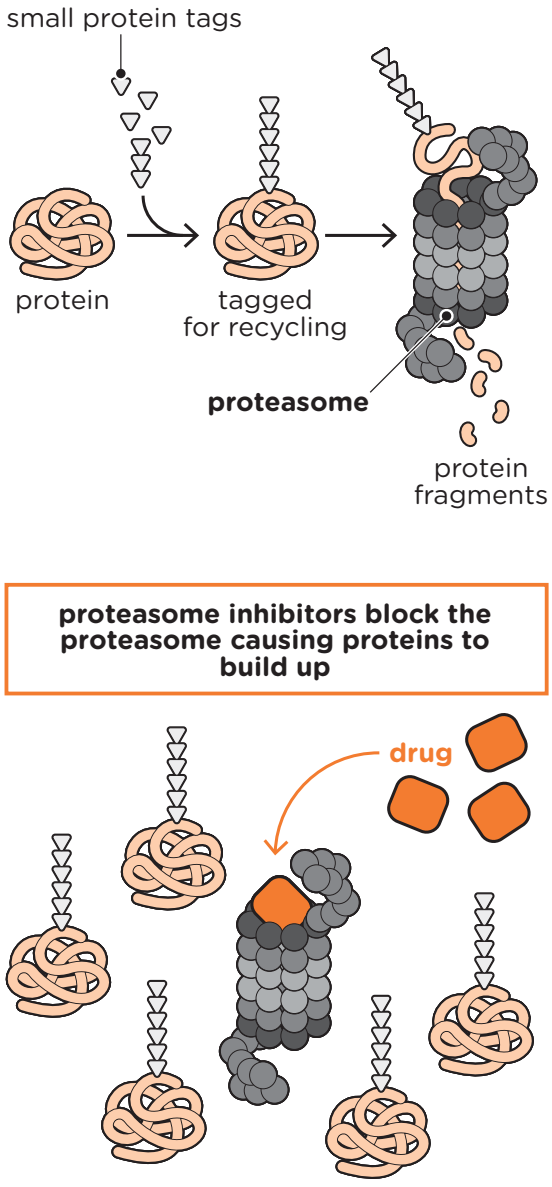

Figure 1. Mechanism of action of proteasome inhibitors

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.

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 (when myeloma has become active again) 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.

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).

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).

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 the UK, ixazomib is currently going through the drugs approval process, which means that, although ixazomib is available to patients in the EU, it is only accessible to UK myeloma patients as part of a clinical trial. However, patients may also access ixazomib through a Compassionate Use Programme (CUP) provided by Takeda, the pharmaceutical company which makes ixazomib.

The CUP means that if a doctor feels that ixazomib is the best available treatment for one of their patients, they can apply to Takeda to receive the drug free of charge. In order to take part in the CUP, patients must fulfil the same eligibility criteria outlined for the Tourmaline-MM1 clinical trial, meaning that they must have

relapsed myeloma and must not be refractory to proteasome inhibitors like bortezomib or lenalidomide.

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.

Other information available from Myeloma UK

Myeloma UK has a range of Essential Guides, Infoguides and Infosheets available covering many 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 the **Myeloma Infoline: 0800 980 3332** or **1800 937 773** from Ireland.

The Myeloma 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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