HEALTH TECHNOLOGY BRIEFING
NOVEMBER 2019

Palovarotene for episodic and chronic use in fibrodysplasia ossificans progressiva – first line

| NIHRIO ID | 10300 | NICE ID | 10249 |
| Developer/Company | Ipsen Ltd | UKPS ID | 652641 |

Licensing and market availability plans
Currently in phase III clinical trials.

SUMMARY

Palovarotene is in clinical development for episodic and chronic use in the prevention of heterotopic ossification (HO) in patients with fibrodysplasia ossificans progressiva (FOP). FOP is a disabling condition, caused by the formation of bony bars within the muscles of the body (HO). This bone formation is usually first noticed in early childhood as a series of hard lumps in the neck or along the spine. These lumps, which may be tender, gradually shrink in size as the affected muscles are replaced by bone. The appearance of bony lumps in muscles is usually spontaneous but can also be provoked by any injury to the muscles.

Palovarotene is an oral, once-daily medicine which attaches to a receptor in cells, called the retinoic acid receptor gamma, switching on processes that reduce bone formation. If licensed, palovarotene has the potential to prevent HO in patients with FOP, a condition for which the only available treatments are for symptomatic relief.
PROPOSED INDICATION

Prevention of heterotopic ossification for patients with fibrodysplasia ossificans progressiva for episodic and chronic use – first line.¹

TECHNOLOGY

DESCRIPTION

Palovarotene (IPN60120, RG-667) belongs to a class of medicines known as retinoids. It attaches to another receptor in cells, called the retinoic acid receptor gamma, switching on processes that reduce bone formation. Palovarotene is therefore expected to help prevent the abnormal bone formation seen in fibrodysplasia ossificans progressiva (FOP) and relieve the symptoms of the condition.¹

Palovarotene is currently in clinical development for the prevention of heterotopic ossification for patients with FOP for episodic and chronic use. In the phase III clinical trial (NCT03312634), patients are administered a chronic dosing regimen of 5 mg palovarotene once daily for 24 months, and a flare-up dosing regimen of 20 mg palovarotene orally once daily for 4 weeks (28 days) followed by orally administered 10 mg palovarotene once daily for 8 weeks (56 days). The flare-up treatment may be extended until the investigator determines that the flare-up has resolved.²

INNOVATION AND/OR ADVANTAGES

Bone morphogenetic proteins (BMPs) are part of the transforming growth factor β (TGF-β) known to regulate various cellular activities such as differentiation and proliferation and are particularly involved in fibrosis. Palovarotene exerts its action on bone formation through the regulation of the BMP pathway by binding of any of several extracellular BMP ligands such as BMP 2, 4, 7 and 9 to the BMP receptor which is membrane bound.³ Palovarotene is expected to help prevent the abnormal bone formation seen in FOP, a condition for which no satisfactory methods of treatment have been authorised in the EU, with patients mainly managed by avoidance of injuries that could trigger a flare-up, and treatment of the symptoms including anti-inflammatory medicines for the pain and inflammation.⁴

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Palovarotene does not currently have a Marketing Authorisation in the EU/UK for any indication.

Palovarotene is in phase II clinical development for multiple osteochondromas.⁴

Palovarotene has the following regulatory designations/ awards:

- Orphan Drug status, awarded by the EMA in November 2014 for the treatment of FOP and multiple osteochondromas.¹
- Breakthrough Therapy, awarded by the FDA in 2017 for the prevention of HO in patients with FOP.⁵

¹ Information provided by Ipsen Ltd on UK PharmaScan
Fibrodysplasia ossificans progressiva (FOP), also known as myositis ossificans progressiva, is a disorder in which muscle tissue and connective tissue such as tendons and ligaments are gradually replaced by bone (ossified), forming bone outside the skeleton (extra-skeletal or heterotopic bone) that constrains movement. This process generally becomes noticeable in early childhood, starting with the neck and shoulders and proceeding down the body and into the limbs. Extra-skeletal bone formation causes progressive loss of mobility as the joints become affected. Inability to fully open the mouth may cause difficulty in speaking and eating. Over time, people with this disorder may experience malnutrition due to their eating problems. They may also have breathing difficulties as a result of extra bone formation around the rib cage that restricts expansion of the lungs. Any trauma to the muscles of an individual with FOP, such as a fall or invasive medical procedures, may trigger episodes of muscle swelling and inflammation (myositis) followed by more rapid ossification in the injured area. Flare-ups may also be caused by viral illnesses such as influenza. People with FOP are generally born with malformed big toes. This abnormality of the big toes is a characteristic feature that helps to distinguish this disorder from other bone and muscle problems. Affected individuals may also have short thumbs and other skeletal abnormalities. 

FOP is caused by spontaneous mutations, predominantly in the ACVR1 gene. The ACVR1 gene provides instructions for producing a member of a protein family called bone morphogenetic protein (BMP) type I receptors. The ACVR1 protein is found in many tissues of the body including skeletal muscle and cartilage. It helps to control the growth and development of the bones and muscles, including the gradual replacement of cartilage by bone (ossification) that occurs in normal skeletal maturation from birth to young adulthood. Researchers believe that a mutation in the ACVR1 gene may change the shape of the receptor under certain conditions and disrupt mechanisms that control the receptor’s activity. As a result, the receptor may be constantly turned on (constitutive activation). Constitutive activation of the receptor causes overgrowth of bone and cartilage and fusion of joints, resulting in the signs and symptoms of FOP. 

There is no ethnic, racial, gender, or geographic predilection to FOP. The median lifespan is approximately 40 years of age. Most patients are wheelchair-bound by the end of the second decade of life and commonly die of complications of thoracic insufficiency syndrome.

FOP is an extremely rare disease, which has a worldwide prevalence of 0.05/100,000. The company (Ipsen Ltd) has estimated that there are circa 80 patients living with FOP in the UK. The Hospital Episodes Statistics for England 2018/2019 recorded 60 finished consultant episodes (FCE), 57 hospital admissions, 42 FCE bed days and 42 day cases for myositis ossificans progressiva (ICD 10 code M61.1).
PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are no known effective treatments for FOP. Certain types of drugs have been used to relieve pain and swelling associated with FOP during acute flare-ups (most notably corticosteroids) and non-steroidal anti-inflammatory medication between flare-ups.\textsuperscript{10}

Affected individuals may benefit from occupational therapy. Special shoes, braces, and other devices that assist in walking and weight-bearing have been used to help people with FOP. Affected individuals may have their physicians contact an occupational therapist who can help obtain special devices or tools to assist them in daily activities.\textsuperscript{10}

Genetic counselling may be of benefit for families with the hereditary form of FOP. A team approach for infants with this disorder will also be of benefit and may include special social, educational, and medical services. Other treatment is symptomatic and supportive.\textsuperscript{10}

CURRENT TREATMENT OPTIONS

When flare-ups begin, a brief 4-day course of high-dose corticosteroids such as prednisone can be used to relieve inflammation and tissue oedema, but corticosteroids can only be used to relieve inflammation in areas such as the mandibular joint. The frequent use of corticosteroids to treat swelling in the trunk and neck is not recommended due to the difficulty in assessing the onset of flare-ups.\textsuperscript{11}

When corticosteroids are discontinued, mast cell inhibitors, aminobisphosphonates, non-steroidal anti-inflammatory drugs, and COX-2 inhibitors could be used to treat later flare-ups. A small dose of a muscle relaxant may help to relieve muscle spasms.\textsuperscript{11}

Clinically, steroids, non-steroids, and anti-inflammatory drugs can mitigate inflammation and pain, but they cannot reduce the frequency of HO.\textsuperscript{11}

PLACE OF TECHNOLOGY

If licensed, palovarotene has the potential to prevent HO in patients with FOP, a condition for which the only available treatments are for symptomatic relief.

CLINICAL TRIAL INFORMATION

<table>
<thead>
<tr>
<th>Trial</th>
<th>MOVE; NCT03312634, Eudra CT 2017-002541-29; aged 4 years or older; palovarotene chronic /flare-up dosing regimen; phase III</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Clementia Pharmaceuticals Inc.</td>
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<tr>
<td>Status</td>
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<tr>
<td>Source of Information</td>
<td>Trial registr\textsuperscript{ies}.\textsuperscript{2,12}</td>
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<tr>
<td>Location</td>
<td>Five EU countries (incl UK), USA, Canada and other countries.</td>
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<tr>
<td>Design</td>
<td>Single group assignment, open label.</td>
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<tr>
<td>Participants</td>
<td>N=90 (planned); aged 4 years and older; clinically diagnosed with FOP, with the R206H ACVR1 mutation or other FOP variants reported to be associated with progressive HO; no</td>
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</table>
flare-up symptoms within the past 4 weeks, including at the time of enrolment.

**Schedule**

Subjects will receive 5 mg palovarotene once daily for up to 24 months; and 20 mg palovarotene once daily for 28 days, followed by 10 mg for 56 days for flare-ups. Dosing will be adjusted for weight in skeletally immature subjects.

**Follow-up**

Up to two years.

**Primary Outcomes**

Change in New HO Volume [Time Frame: Screening, every 6 months up to 2 years]

**Secondary Outcomes**

Time frame every 6 months up to two years:

- Subjects with new HO: the proportion of subjects with any new HO

Time frame: screening, every 6 months up to two years:

- Number of body regions with HO: change from baseline in the number of body regions with new HO

Time Frame: Up to 2 years:

- Subjects with flare-ups: the proportion of subjects reporting flare-ups
- Rate of flare-ups: the rate of flare-ups per subject-month exposure
- Incidence of adverse events: monitor adverse events

Time Frame: pre-dose, and 3, 6, 10, and 24 hours post-dose:

- Palovarotene area under the curve (AUC): determination of AUC at steady-state assessed during treatment with 5, 10, and 20 mg palovarotene

**Key Results**

Not reported.

**Adverse effects (AEs)**

Not reported.

**Expected reporting date**

Estimated primary study completion date reported as September 2020. Estimated study completion date reported as November 2020.

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**ESTIMATED COST**

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**RELEVANT GUIDANCE**

**NICE GUIDANCE**

None identified.
NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

None identified.

OTHER GUIDANCE


ADDITIONAL INFORMATION

REFERENCES


*NB:* *This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.*