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# Vosoritide, a miracle drug, covering unmet need in achondroplasia: A regulatory update

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**SUMMARY** Dwarfism is a rare condition characterized by small stature. Achondroplasia is predominantly considered the leading cause of dwarfism. Although the condition is not life-threatening, it dramatically impacts the social life of the patient. The United States Food and Drug Administration (US FDA) first approved the drug Voxzogo (vosoritide) for achondroplasia. The drug also received approval from the European Medicines Agency (EMA) *via* the centralized procedure. The drug is associated with a decrease in blood pressure, a severe adverse event. However, this adverse event/risk has been overcome by benefits, *i.e.* fulfilling of unmet medical need. In the United States, the drug received accelerated approval as it satisfied the criteria of rare pediatric disease. This review includes a detailed orphan drug approval process with particular reference to vosoritide, which is considered a milestone for the treatment of achondroplasia.

***Keywords*** US FDA's Orphan Products Grants Program, European Medicines Agency, vosoritide, achondroplasia, rare disease

## 1. Introduction

Rare diseases are diseases that affect only a small population. The definition of rare diseases varies from country to country based on their population. As per 10,000 people, a prevalence of less than 6.4 is considered rare disease in the United States (US); whereas a prevalence of less than 5 in European Union (EU) and Canada, and less than 4 in Japan and South Korea is regarded as the criteria for rare disease. Due to the lack of epidemiological data, prevalence-based definition has not been established yet in India (*1*). These rare diseases can be classified into two categories: life-threatening rare diseases and non-life-threatening rare diseases based on their severity. Tyrosinemia and lysosomal storage disorder are examples of life-threatening rare diseases. On the other hand, galactosemia and dwarfism are considered non-life-threatening diseases.

The drugs that are used in the treatment of rare diseases are called orphan drugs. Around 7,000–8,000 rare diseases have been identified so far and out of these only 5% have approved treatments. Disease specific treatment have been made available to a very marginal amount of patients, *i.e.*, less than 1 in 10 (*1*). There are multiple reasons for the unavailability of treatment for rare diseases. Among them, from the pharmaceutical company's perspective, the primary ones include less targeted population, more investment to study discrete physiological functions, less profit, and difficulty in conducting clinical trials in a small population. Whereas, from the regulatory bodies' perspective, separate guidelines for clinical trials related to rare diseases, less collaboration with pharmaceutical companies, and a weak framework of regulations regarding rare diseases are the major reasons. Apart from this, although treatment is available, it is not affordable by the patients.

Vosoritide is considered a milestone in treating dwarfism associated with achondroplasia: a genetic disorder in which mutation occurs in the fibroblast growth factor receptor 3 (FGFR3) gene responsible for converting cartilage into bones especially in the long bones of the arms and legs. In the US, fewer than 50,000 people are suffering from achondroplasia, making this a rare disease (*2*). Dwarfism has been recognized since ancient years, and evidence for the same can be found in the artworks of Rome, Greece & Egypt. The term achondroplasia was used in the first place about 100 years ago by Jules Parrot, a noteworthy figure in French pediatrics. However, previously dwarfism was not considered a disease, but now it has been included in the rare disease list of the United States (*3*). Achondroplasia is the primary and most common cause of dwarfism worldwide.

## 2. Achondroplasia

Achondroplasia is an autosomal-dominant disorder which is caused by change or mutation on the transmembrane portion of the FGFR-3 gene. In the mutation process, a glycine amino acid is replaced by arginine (G380R or Gly380Arg) at protein position 380 of the gene FGFR-3. Mutation at Gly380 leads to a 100% chance of achondroplasia, whereas mutation at Gly375 may lead to achondroplasia. The term achondroplasia literally implies the meaning: "without cartilage formation". Ossification, or the process of turning cartilage into bone, is the concern with achondroplasia, notably in the long bones of the arms and legs (*4*). A diagrammatic representation of the mutation sites for achondroplasia has been given in Figure 1.

Diagnosis of achondroplasia can be made through radiological and clinical feature analysis (*5*). Apart from the shortage of limbs, the disorder may also lead to other health conditions i.e, lordotic lumbar spine, apnea (breathing interruptions), ear infections, obesity, spinal stenosis and hydrocephalus (fluid build in the brain). Some studies also state that it impacts the lifespan of the patient.

In Japan, growth hormone is administered in the treatment of achondroplasia, which shows efficacy for up to 2 years, but many health complications are associated with it. An alternative to the former is a limb elongation procedure, which is also controversial (*6*). Vosoritide is a drug recently approved by both United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) for treating achondroplasia.

## 3. Vosoritide

Vosoritide resembles C-type natriuretic peptide (CNP) made up of 39 amino acids. Vosoritide binds to Natriuretic Peptide Receptor B (NPR-B), activates it and restores chondrogenesis, a process through which cartilage is developed. The chemical structure of vosoritide and C-type natriuretic peptide (CNP) is given in Figure 2. Activation of NPR-B leads to inhibition of the downstream signaling of the gene FGFR-3. Downstream signaling of the FGFR-3 gene inhibits proliferation and differentiation in bones leading to dwarfism. Vosoritide inhibits Rapidly Accelerated Fibrosarcoma Kinase-1 and by this promotes proliferation and differentiation within bones leading to the cure of dwarfism. The diagrammatic representation of the mechanism of vosoritide is given in Figure 3.

## 4. Regulatory approval aspects of the drug

Vosoritide received marketing authorization approval under the category of orphan drugs by EU and the US. Both the countries have different guidelines regarding the approval process of orphan drugs. In the EU, nearly 36 million people have been affected by more than 6,000 rare diseases. Of these, 80% are genetic, and around 70% develop in the pediatric stage. This accounts for the fact that 60% of orphan drugs are pediatric. According to EMA, a drug used in the treatment, prevention or diagnosis of a severe and life-threatening or chronically debilitating disease, affecting not more than 5 in 10,000 people is considered an orphan drug. The drug should also demonstrate significant benefit to any existing method of diagnosis, treatment or prevention of the condition (*7,8*). EMA assigns Committee for Orphan Medicinal Products (COMP) to examine whether the drug fulfills the criteria of being designated an orphan drug in the EU. The committee takes 90 days to evaluate the same.

The drug sponsor is eligible for a range of incentives and fee reductions which would encourage them to develop orphan drugs for rare diseases. EMA also offers scientific advice or protocol assistance, which aids the

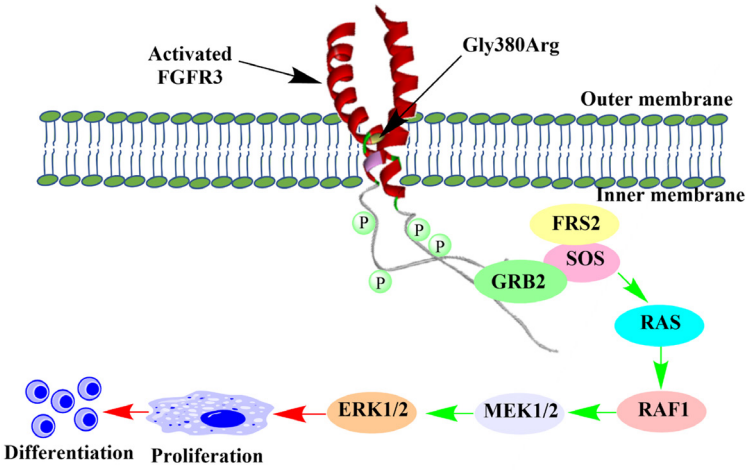


**Figure 1. Mechanism of achondroplasia.** Green arrow shows initiation; Red arrow shows inhibition. FGFR3: fibroblast growth factor receptor 3, Gly380Arg: mutated amino acid, GRB2: growth factor receptor-bound protein 2, FRS2: fibroblast growth factor receptor substrate 2, RAF1: raf-1 kinase, MEK1/2: mitogen-activated protein kinase kinases 1 and 2, ERK1/2: extracellular signal-related kinases 1 and 2, cGMP: cyclic guanidine monophosphate.

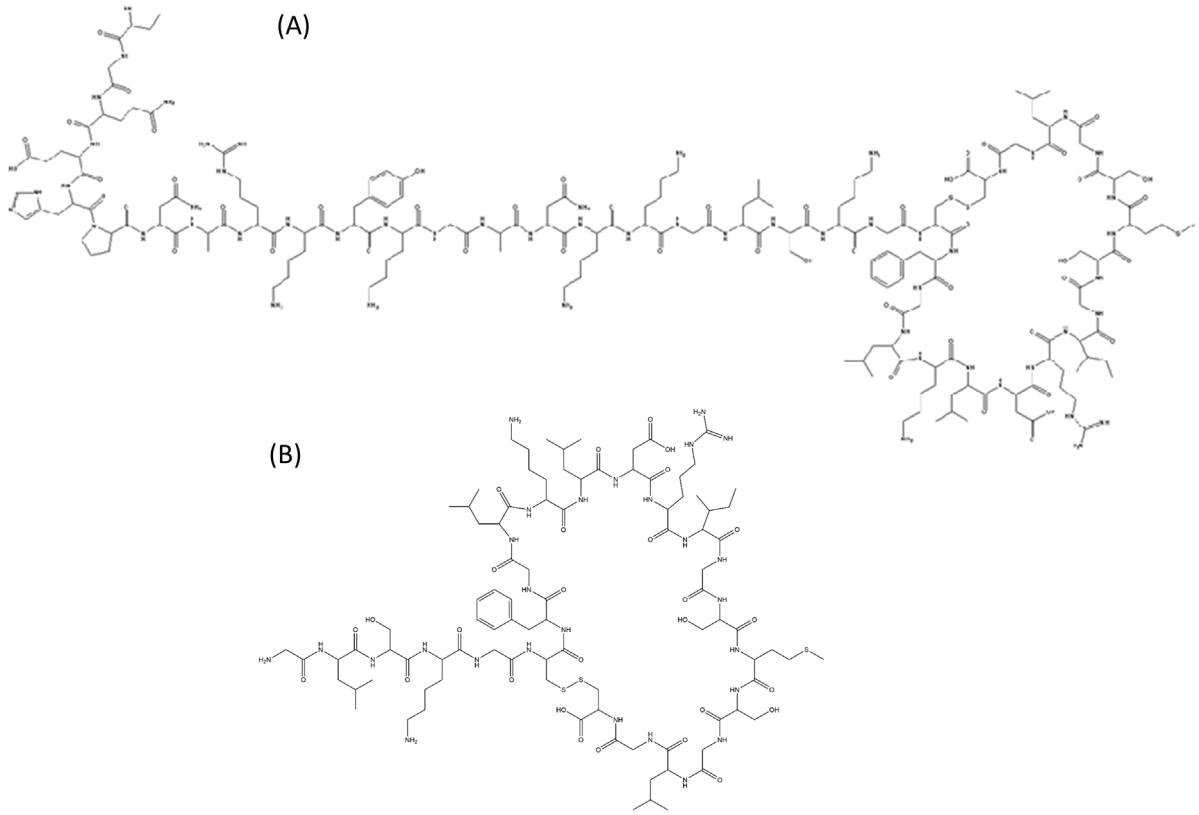


**Figure 2. Chemical structure of (A) vosoritide and (B) C-type natriuretic peptide (CNP).**

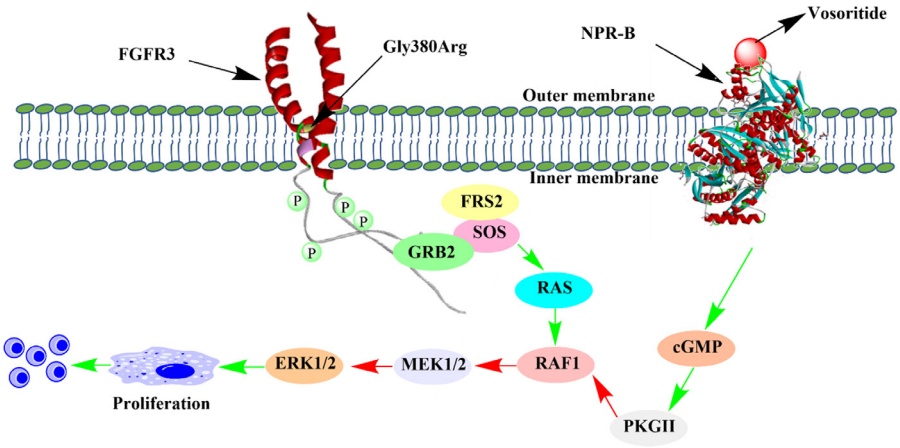


**Figure 3. Mechanism of action of vosoritide on achondroplasia.** Green arrow shows initiation; Red arrow shows inhibition. FGFR3: fibroblast growth factor receptor 3, Gly380Arg: mutated amino acid, GRB2: growth factor receptor-bound protein 2, FRS2: fibroblast growth factor receptor substrate 2, RAF1: raf-1 kinase, MEK1/2: mitogen-activated protein kinase kinases 1 and 2, ERK1/2: extracellular signal-related kinases 1 and 2, cGMP: cyclic guanidine monophosphate.

sponsor concerning quality, clinical, non-clinical aspects, and overall development strategy of the drug. In the case of micro, small and medium sized enterprises (SMEs), a fee reduction of up to 90% is applicable (*9*). The most attractive incentive offered by the European Commission to pharmaceutical companies is the 10-year market exclusivity period. This period can be extended by an additional two years if they are used in the pediatric population. Furthermore, orphan drugs have access to a centralized authorization procedure. They are also applicable for conditional approval under centralized procedures (*10*).

According to US FDA Orphan Drug Act, diseases affecting less than 200,000 people are regarded as rare diseases. In the US, 30 million people are affected by over 7,000 rare diseases. Before 1983, pharmaceutical

**Table 1. Comparative table describing the orphan drug designation and incentives offered by EU and US**

| European Union (EU) | United States (US) |
|---|---|
| Prevalence calculation: Less than 5 in 10,000 in whole EU | Prevalence calculation: Less than 200,000 people in the US |
| 10 years market exclusivity period (extended to 12 years if pediatric investigation plan fulfilled and implemented) | 7 years market exclusivity period |
| EMA provided no funding. | Funding provided by US FDA |
| 200 marketed orphan drug | 100 approved orphan drug |
| Incentives applicable to only very serious and life-threatening, chronically debilitating disease | Incentives applicable to all kinds of rare diseases listed in the US |
| Pathways: Centralized marketing authorization and conditional approval | Pathways: Accelerated and prior approval |
| Waiver or fee reductions for marketing authorization application | Exemption from user fees for marketing application |

companies had displayed no interest in developing orphan drugs as it was a very challenging task. This was because of the inherently low patient population, high cost of drug development, and the challenge in conducting clinical trials. In 1983, the US FDA developed the Orphan Drug Act which attracted drug developers as it provided incentives for orphan drug development. The sponsors can apply for various incentives such as a 7 year market exclusivity period after approval, tax credits for clinical testing, and Prescription Drug User Fee waiver (*11*).

Moreover, the US FDA also provides funding to the orphan drug developers through the Orphan Products Grants Program. This program has supported and funded clinical trials since 1983 and has assisted in approval of more than 80 products. The US FDA provides priority review vouchers for rare pediatric disease sponsors according to Section 529 of the Federal Food, Drug, & Cosmetic Act, which was added by the Food and Drug Administration Safety and Innovation Act (FDASIA). On 14th October 2021, the US FDA awarded 11 research grants for conducting clinical trials for rare diseases (*12*). Moreover, nowadays researchers are focusing on multiple unique approaches to develop treatment of rare diseases. In early 2023, in silico approach developed the first artificial intelligence treatment for idiopathic pulmonary fibrosis, which is a rare disease. This treatment reached up to phase II clinical trial in the US (*13*). The plant extract cannabidiol was also found to be effective in Dravet syndrome (rare epilepsy), which is also considered a rare disease. Achondroplasia is listed as a rare disease by the National Organization for Rare Disorders (NORD), which is an American non-profit organization. According to NORD, nearly 1 in 15,000 to 30,000 births are affected by achondroplasia in the US (*15*). On 19$^{th}$ November 2021, the US FDA approved the first treatment for Achondroplasia. The drug, Vosoritide has been approved through an accelerated approval pathway because the drug accomplished the unmet medical need of the disease (*16*). The application also went through prior approval, but final approval was sought through the accelerated approval pathway. Accelerated drug approval is provided based on the surrogate endpoint in clinical trials. For instance in cancer treatment, the sponsor cannot wait until evidence has been generated that the drug extends survival (clinical endpoint) in patients and so the agency can approve the drug based on the evidence that the treatment shrinks tumours (surrogate endpoint) (*17*).

A comparison between the orphan drug designation criteria and the incentives offered in the EU and the US has been given in Table 1. After comparing the regulations regarding orphan drugs in the two countries, it is observed that the EU has approved 200 drugs for rare diseases, which is double compared to the US. Although EMA does not provide funding directly and also considers only serious, life-threatening and chronically debilitating disease treatment under orphan designation, it still offers 10-year exclusivity for orphan drugs, which attracts many pharmaceutical companies towards it.

In August 2021, EU was the first country that approved vosoritide to treat achondroplasia in children aged ≥ 2 years with open epiphysis (*18*). The approval was given through a centralized procedure because the drug fulfilled all the requirements needed (*19*). 35 participants were enrolled in the 2nd phase of clinical trial, and during the 30-month cohort study, there were no severe adverse effects observed in participants. The trial was carried out in children aged 5 to 14 years (*20*).Moreover, in the 3rd phase of clinical trial, 119 participants entered into an extensive open-label study after placebo. No new adverse event was noticed in the 3rd clinical trial for a duration of up to 2 years (*21*).

## 5. Conclusions

Pharmaceutical companies are afraid to develop orphan drugs due to low targeted population and high investment. Moreover, the exclusive exemptions, fee waivers and patent exclusivity provided by the regulatory bodies encourage the companies to work on

orphan drugs. However, most of the researchers work on life-threatening rare diseases. Approval of vosoritide opens the path for the development of other non-life-threatening rare disease treatments. Approximately 6,000 rare diseases are in the EU and there are only 200 approved orphan drugs. Moreover, in the US there are only 100 approved orphan drugs. This data emphasized a huge gap in the disease and treatment in the case of rare diseases. More incentives and collaboration between the regulatory bodies and pharmaceutical companies are required to fill the gap.

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